Amesthesia and Amalgesia

Journal of the International Anesthesia Research Society Oldest Publication in the Specialty—Established 1922



In neuromuscular blockade

Norcuron

(vecuronium bromide) for injection

Minimizes the variables



 ∇ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease^{1,2}



∇ NORCURON* requires no dosage adjustments to avoid histamine release



May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment³⁴

P, 24, 549

As with all drugs in this class, NORCURON* should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There is no services.
There is no becaused

~ Cule-H02983-37-p024549

Norcuron (vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known
WARNINGS NORCURONS SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE
SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR POLLOWING ITS USE THE DRUG SHOULD NOT BE ADMINISTERED UNLESS
RCILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, DXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are
known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may be
profound effects in such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle reliaxants.
PRECAUTIONS: Renal Fallure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under
emergency conditions in anephric patients some prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under
emergency conditions in anephric patients some prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under
emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur, therefore, it
encephric patients cannot be prepared for nonelective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age,
edemalous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

age should not be increased. **Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time

neparte Disease: Limited experience in patients with crimosts or cholestasts has revealed protinged recovery interesting the recovery interesting

agents such as norcuron[®]. Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially latal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron[®] is capable of triggering

malignant hyperthermia.

Norcuron* has no known effect on consciousness, the pain threshold, or cerebration. Administration must be

malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold, or cerebration. Administration must be accompanied by adequate anesthesia.

Drug interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (everuronit mornide) for injection and its duration of action. If succinylcholine is used before Norcuron® the administration of Norcuron® whold be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent initial doses of 0.04 to 0.06 mg/kg of Norcuron® way be administered to produce complete neuromuscular block with clinical duration of action of 25 to 30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents act in the same tashion as does Norcuron®. Therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetics are been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibloties: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, lenamycin, gentamicin, and dihydrostreptomycin); tetracyclines; hacitracin, polymyxin B. Colitism, and sodium colisimetheties.

Other: Experience concerning injection of

shown to after neuromuscular blockade. Depending on the nature of the imparance either enhancement of imparance either enhancement of the management of toxem and pregended. Magnesium salts, administered for the management of toxem and pregnancy, may enhance the neuromuscular blockade.

Drughaboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility. Pregnancy Category C. Animal reproduction studies have not been conducted with Norcuron® Norcuron® should be given to a pregnant woman only if clearly needed.

Podiatric Use: Infants under 1 year of age but older than? Weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently saviable does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced on adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is used in anesthetic practice which also cause re

DIOCAGE AND ADMINISTRATION: Before prescribing, please consult complete product information.

Norcuron* (vecuronium bromide) for injection is for infravenous use only. Dosage must be individualized in each
use. The dosage information which follows is derived from studies based upon units of drug per unit of body weight
dis intended to serve as a guide only especially regarding enhancement of reuromuscular blockade of Norcuron*
y volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS) Drug Interactions). Parenteral drug
products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container nermit.

in and container permit

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of

muscle (witch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron² is 0.00 to 0.10 m/gg (1.4 to 1.75 times the ED_x) given as an intrawrous bolus mjection. This dose can be expected to produce good or excellent nonemergency intubation conditions
in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts
proximately 25 to 30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection
and recovery to 95% of control achieved approximately 45 to 65 minutes after injection. In the presence of

potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, ie, 0.030 to 0.085 mg/kg. Prior administration of succinyl-choline may enhance the neuromuscular blocking effect and duration of action of Norcuron® if influbation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04 to 0.06 mg/kg with inhalation anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended, after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses. If required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia. slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

signity longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardio-vascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80 to 100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20 to 40 minutes later. Infusion of Norcuron* should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations.

The infusion of Norcuron* should be individualized for each patient. The rate of administration should be adjusted according to the patient's witch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended with the rate of the intustion adjusted threather to maintain a 90% suppression of witch response.

Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enfluence and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25 to 60%, 45 to 60 minutes after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron* infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion rates of Norcuron* can be prepared by mixing Norcuron* with an appropriate infusion solutions should be discarded.

Drug Delivery Rate (µg/kg/min)	Infusion D (mL/k		
0.7 0.8 0.9 1.0 1.1 1.2 1.3	0.1 mg/ml 0.007 0.008 0.009 0.010 0.011 0.012 0.013	0.2 mg/mL* 0.0035 0.0040 0.0045 0.0050 0.0055 0.0060	

10 mg of Norcuron® in 100 mL solution 20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion

NORCURON® Infusion Rate (mL/min)

Amount of Drug	Patient Weight (kg)						
(µg/kg/min)	40	50	60	70 ~	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

Note: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half

Note: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/ kg) as adults and may be managed the same way 'hounger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more ofter than adults Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1.1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous indusion of vecuronium in children therefore no dosing recommendation can be made.

COMPATIBILITY: Norcuron* is compatible in solution with:

0.9% NaCI solution

0.9% NaCI solution

Sterile water for injection,

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: 10 mL vials (10 mg of vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP). 20 gl 1.1/4" needle. Boxes of 10 (NDC #0052-0441-60).

water in injection, D57, 22 g in 74 recoles boxes on 10 (NDC #0052-0441-05).

10 mt. vials (10 mg vecuronium bromide) and 10 mt. vials of diluent (bacteriostatic water for injection, USP). Boxes of 10 (NDC #0052-0441-17).

10 mt. vials (10 mg vecuronium bromide) only. DILUENT NOT SUPPLIED. Boxes of 10 (NDC #0052-0441-15) STORAGE: 157-30°C (59°-85°F). Protect from light.

AFTER RECONSTITUTION:

When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or retrigerated. When reconstituted with sterile water for injection or other compatible I.V. solutions. Refrigerate vial. Use within 24 hours. Single use only Discard unused portion.

References:

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- Lowry KG, Mirakhur RK, Lavery GG, et al. Vecuronium and atracurium in the elderly: A clinical comparison with pancuronium. Acta Anaesthesiol Scand 1985;29:405-408.
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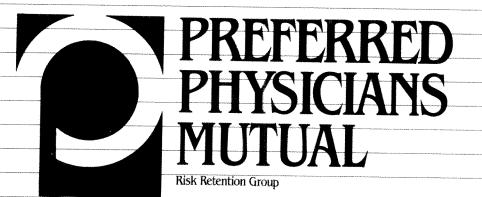
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Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µp per mid alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersentibitive to the drun.

CONTRAINDICATIONS: ALFENTA (altentani hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA (altentani hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID NATAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY ALFENTA (altentani hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at ansethetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of an euromuscular blocking agent is rior to administration of ALFENTA at one that the produce of a neuromuscular blocking agent that the produce of a neuromuscular blocking agent than a truly appraising the produce of a neuromuscular blocking agent than ALFENTA at a sugar larging loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent than ALFENTA and a full paralyzing dose of a neuromuscular blocking agent than the standard paralyzing dose of a neuromuscular blocking agent than ALFENTA and a full paralyzing dose of a neuromuscular blocking agent than ALFENTA and a full paralyzing dose of a neuromuscular blocking agent than the paralyzing dose of a neuromuscular blocking agent to the patients administered ALFENTA. It is

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRAUTCANDIA, ASTSTUCIONED ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA representations of lear hody weight in one clinical trial, the dose of ALFENTA representations of lear body weight. In one clinical trial, the dose of ALFENTA representations of the patients of

respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA. Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of crythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis. Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Amens Saimonella typhimurium metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential irisk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: in one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently

available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory respir

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal						
Nausea	28	44	14	5 9	0 13	22 17
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8 39 7	0 36	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	12 8 13		7	0	0
Hypertension	18	13	30	20	0 6	0 0 0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall	17	12	0	0	0	0
Rigidity			-	-	-	-
Skeletal Muscle	6	2	6	2	0	0
Movements		_		_	-	
Respiratory						
Apnea	7	0	0	0	0	0 '
Postoperative	2	0	Ō	0	Õ	Õ
Respiratory	-	-		0		•
Depression						
CNS						
Dizziness	3	5	0	n	0	n
Sleepiness/	3	5 8	0	ŏ	Õ	6
Postoperative Sedation	-	Ü	-	O	Ü	Ü
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm,

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and irching, Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA. **DRUG ABUSE AND DEPENDENCE:** ALFENTA (alfentanii hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused. **OVERDOSAGE:** Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanii hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analyesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravengus LD₈₀ of ALFENTA is 43.0-50.9 mg/kg in guinea pigs and 69.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of attendance and administration of or oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to lacilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

agent may be required to labilitate assisted or controlled ventilation. Intravenous nulus and vasoactive agents must be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanii hydrochloride) should be individualized in each patient according to body weight, hysical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be effected patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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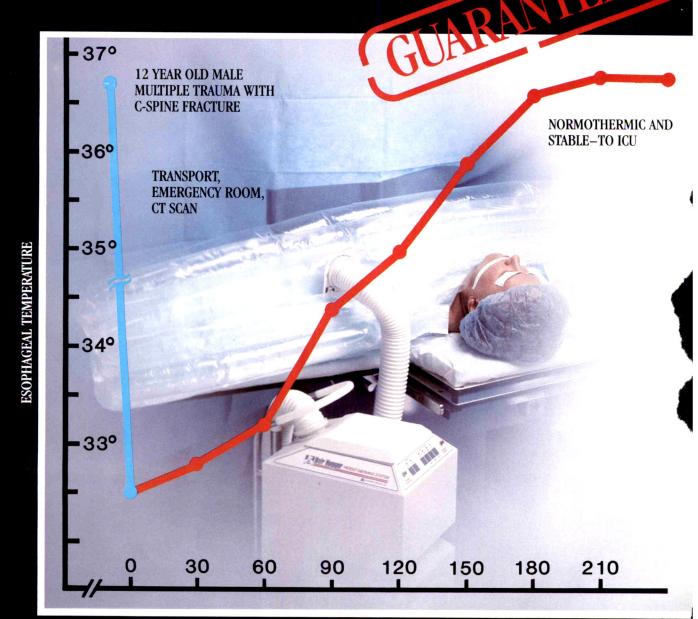
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DESCRIPTION: SUFENTA (sufentant) citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl)-4-piperidinyl]-N-phenylpropanamide 2-nydroxy-12,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile preservative free aqueous solution containing sufentantil citrate equivalent to 50 μg per ml of sufentantil base for intravenous injection. The solution has a pH range of 2.5.6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and certeral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE

DESUPERTA:

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ½ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg.) 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and at ull paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in anesthetic dosages (above 8 μg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxant required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the post-operative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interactions when the receiving barbiturates, such appropriate surveillance when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase arrway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as $80 \,\mu\text{g/kg}$ (approximately 2.5 times the upper human dose) produced no

structural chromosome mutations. The Ames Salmonella typhimurium metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabolis when give in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is on the commendation.

not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous Lb₂₀ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trails involving 20 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 19% were:

Dermatological: teching, erythema

Cardiovascular: tachycardia arrhythmia

Dermatological: itching, erythema Central Nervous System: chills Miscellaneous: intraoperative muscle movement

Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory

Respiratory: apnea, postoperative respiratory depression, bronchospasm
DRUB ABUSE AND DEPENDENCE: SUFENTA (sufentanii citrate) is a Schedule II controlled drug substance that
can produce drug dependence of the morphine type and therefore has the potential for being abused.
DVEROUSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA
(see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage
with SUFENTA have been established during clinical trials. The intravengus LD₅₀ of SUFENTA in male rats is 9.34 to
12.5 mg/kg (see ANIMAL TOXICOLOGY for LD₅₀S in other species). Intravenous administration of an opioid antagonist
such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of
respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid
antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the
event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may
be indicated, if depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be
required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of
hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to
body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure
and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be
determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see
PRECAUTIONS), Vital signs sh

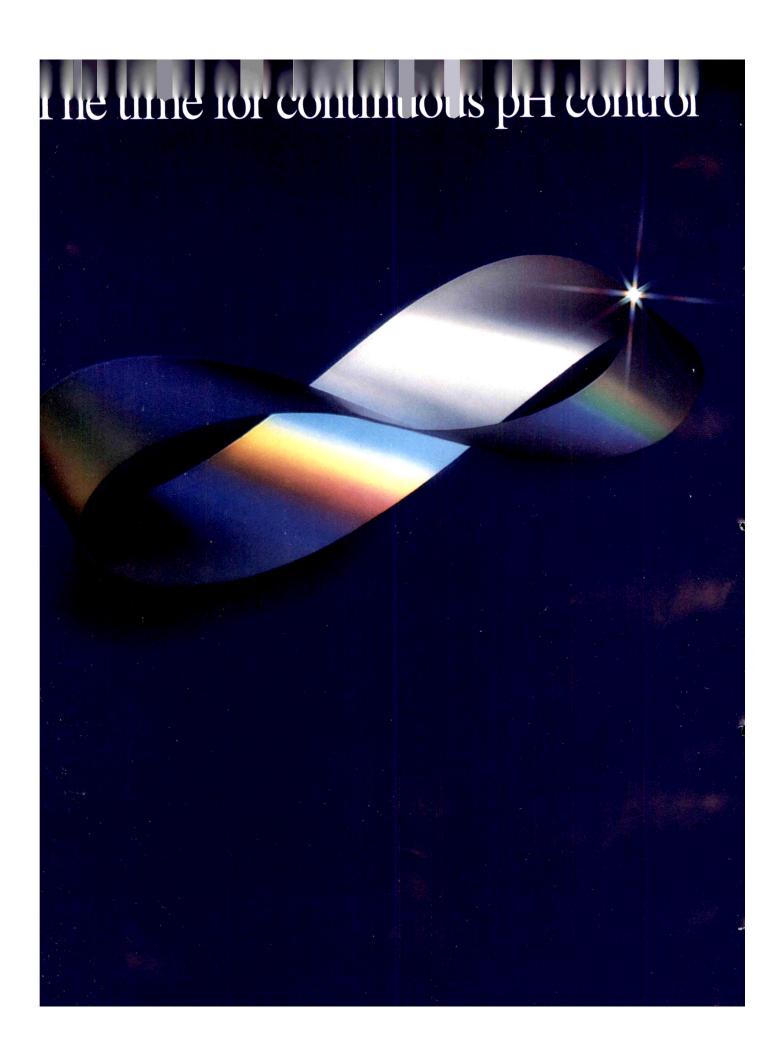
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Symptomatic response to "lagamet" therapy does not preclude the presenc of a gustric mallignancy. There have been rare reports of transient healing o gustric ulcers despite subsequently documented mallignancy.

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

In severally in pacter is. They amen't has been reported to reduce the hepatic metabolism of warfarin-type anticoagularias, phenydoin, propranciol, chlordazepowice, disrepant, certain tricyclic anticlepressants, idiocaine, theophylinine and metronidatolic Chriscally significant effects have been reported with the warfarin anti-coagularias; therefore, dose monitoring of prothrombin time is recommended, and adjustment of the anticoagularia dose may be necessary when "ligames" is administrated concomitantly interaction with phenydoin, idiocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either "Regenet" 300 mg 4,d. or 800 mg h.s. concomitantly with a 300 mg b.d. dosage of the orbital file of the orbital file of the orbital file orbital file

in a 24-month toxicity study in rats, at close levels approximately 8 to 48 times to recommended human dose, benign Leydig cell tumors were seen. These were common in both the restated and control groups, and the incidence became significantly higher only in the aged rats receiving "Degamet".

A weak antiandrogenic effect has been demonstrated in animals. In human studies, "Bigarnet" has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pregnancy Category B: Reproduction studies have been performed in rats, nobits and mice as doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fests due to 'Regame'. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lack of experience to date precludes recommending "Bigamet" for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since chriefdine is secreted in human milk.

generally, nursing should not be undertaken by patients taking the drug since of metidine is secreted in human milk.

Advance Resectiones Diarries, dizaness, somnolence, headache, Reversible confusional states leg., mental confusion, aptation, psychosis, depression, ensiety, hallucinations, disorbertation), percolaminative in severely ill patients, have been reported. Reversible impotence in patients with pathological dypersecretory disorders receiving "Regiment", particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population. Gyneconastial has been reported in patients treated for one month or longer. Decreased white blood cell counts in "Regarder-treated patients (approximately 3 per million patients), have been reported in patients treated for one month or longer. Decreased white blood cell counts in "Regarder-treated patients (approximately 3 per million patients), have been reported in patients who had serious concomitant Rinesses and received drugs and/or unstatent known to produce neutropenia. Thrombocytopenia paproximately 3 per million patients) and, very rarely, cases of aphasic anemia have also been reported increased series Receases of the predominance of tholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient secentral Raginese has been reported. Increased plasma creations in a battern seconds; in an existing analysis and retension, particular, in the been reported. Increased plasma creations in a patient secentral Raginese of the predominance of tholestatic features, severe parenchymal injury is considered highly unlikely. A single case of biopsy-proven periportal hepatic fibrosis in a patient secentral Raginese of the predominance of tholestatic features, severe payment inscribing anaphysista and retensible arthrishja, myalgia and exacutation of joint s

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1. Frank VI, Kartstadt R. Rockhold F, et al. Comparison between continuous and intermittent infusion regimens of cimeticine in user patients. Cft. Phrammacol Ther. 1989;46:234-239, 22. Ostro MJ, Russell JA, Soldin SI, et al. Control of gastric pH with checkdine: Bobases versus primed infusions. Gastroeneonlogy. 1985;89:532-537. 3. Baptista RJ. Role of histamine first-preceptor inatagonists in total parenteral nutrition patients. Am J Med 1987; 83(suppl 6 A):533-57.

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Fractium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous intusion through the same needle. Depending on the resultant pH of such mixtures. Tractium may be inactivated and a free acid may be

PRECAUTIONS:

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exer cised in administering Tractium to patients in whom substantial histamine release would be especially hazard-ous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactor actions or astmal suggesting a greater risk of histamine release. In these patients, the recommended initial Trachum dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided coses over one minute

Since Tractium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia

outline act the proportional produced by harry arrestment agents or right standard and a resolution and during anesthesia may be more common with Tracrum than with other muscle relaxants.

Tracrum may have protound effects in patients with myasthenia gravis. Eaton-Lambert syndrome or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral

neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hypertherima (MH), a potentially datal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients, however, since MH can develop in the absence of established triggering agents in the clinician should be prepared to recognize and treat MH any patient schedulect for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible patients, fracrium did not trigger this syndrome.

Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.

The safety of Tracrium has not been established in patients with bronchial asthma

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tractium include enflurane, isoflurane halothane certain antibiotics, especially the aminoglycosides and polymyxins, lithium, magnesium salts, procainamide, and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect.

should be considered

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may in-crease the depth, of neuromuscular blockade induced by Tractrum. Tractrum should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis. Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the letus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No

harmful effects were attributable to fractium in any of the newborn infants, although small amounts of fractium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been adamays as a consumer of the management of the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when fractium is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic Most adverse reactions were of time clinical significant energy in the wave associated with significant herisoynetic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients without cardiovascular disease, were as follows in those patients given the recommended initial dosage range of 0.3 to 0.50 mg/kg of fractium, mean arterial pressure increased in 2.8% and decreased in 2.7% of patients white the heart rate increased in 2.8% of these patients. At doses of ≥ 0.6 mg/kg, 1.4% of the studied patients had a decrease in mean arterial pressure white 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6%. and decreased in 0.3% of these patients

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately Ubserved in Canaca Practice: Based bit Limital experience in the ordinary on ordinary more organization applications. Smillion patients given fracroum the following adverse reactions are among the most frequently reported. General altergic reactions (anaphylactic or anaphylaction) which in rare instances, were severe (e.g., cardiac arest), Musculoskeletal, madequate, prolonged block, Cardinascular, hypotension, vasodilatation (flushing), tachy-cardia, bradycardia. Respiratory dyspinea bronchospasm, laryngospasm, Integrimentary rash, unlicaria, in-

STORAGE. Tracrium Injection should be refrigerated at 2°to 8°C (36° to 46°F) to preserve botency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

Miller R. Rupo S. Fisher D. et al. Clinical pharmacology of vecuronium and atracurium. *Anesth* 1984; 61:444-453. Payne J. Atracurium. in Katz R (ed.). *Muscle Relaxants: Basic and Clinical Aspects.* Orlando, Grune & Stratton.

Eagar B Flynn P Hughes R. Infusion of atracurium for long surgical procedures. Br J Anaesth 1984-56-447-452

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Transplantation of the Liver

Edited by Willis C. Maddrey. MD, Magee Professor of Medicine. Chairman of the Department of Medicine. Jefferson Medical College. Thomas Jefferson University, Philadelphia

With 35 contributors

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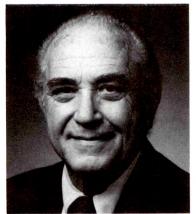


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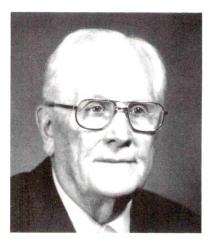


Arthur S. Keats, MD

Chief, Division of
Cardiovascular Anesthesia,
Texas Heart Institute;
Clinical Professor of Anesthesiology,
University of Texas, Houston

The ASA Distinguished Service Award he received in 1984 was richly deserved recognition of his many contributions to the Specialty. A preeminent cardiac anesthesiologist and educator, Dr. Keats has also served as editor in chief of "Anesthesiology" and president of the American Board of Anesthesiology. The IARS honors him as well with our invitation to present this T.H. Seldon Distinguished Lecture. He honors us doubly by his acceptance.

The Lecture to be given by Dr. Keats is the eighth such to honor Dr. "Harry" Seldon, who served as Editor of *ANESTHESIA* and *ANALGESIA* for 23 years ending in 1977.



T.H. Seldon, MD, FFARCS(I) Rochester, Minnesota

Sciatic Nerve Blocks in Children: Comparison of the Posterior, Anterior, and Lateral Approaches in 180 Pediatric Patients

Bernard Dalens, мо, Alain Tanguy, мо, and Guy Vanneuville, мо

DALENS B, TANGUY A, VANNEUVILLE G. Sciatic nerve blocks in children: comparison of the posterior, anterior, and lateral approaches in 180 pediatric patients. Anesth Analg 1990;70:131–7.

Three techniques for blocking the sciatic nerve, differing in approach (posterior in group P; lateral in group L; and anterior in group A), were prospectively evaluated in 180 children who were also given light general anesthesia for surgery below the knee. Four anesthetic solutions with epinephrine (1% lidocaine, 0.5% bupivacaine, and two mixtures of 0.5% bupivacaine with either 1% lidocaine or 1% etidocaine) were administered to 15 patients in each group. The sciatic nerve was located by electrical stimulation or, when muscle twitches were not elicited, using a loss-of-resistance technique. Twitches were "typical" in 154 patients of whom 153 developed sciatic nerve block. In 26 patients twitches were atypical (eight patients) or absent (18 patients) and a sciatic block developed in only 13 patients

(50%). The depth to which the needle was inserted was measured in each procedure; it varied according to patient's age and weight and was significantly less with the posterior approach than with either the lateral or anterior routes. The overall success rate exceeded 90% in the three groups but significantly fewer difficulties were encountered in group P than in group A. Although the spread of the anesthetic was different in the three groups, the distribution of anesthesia in the lower extremity was similar, including not only dermatomes supplied by the sciatic nerve, but also those supplied by the posterior femoral cutaneous nerve. No neurological sequelae were observed. It is concluded that the posterior and lateral approaches are the most suitable in children for blocking the sciatic nerve proximally.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—sciatic nerve block. ANESTHESIA, PEDIATRIC.

Sciatic nerve block is a well-established procedure, even in children. However, even though several techniques have been reported for using it alone or in combination with femoral and/or lateral femoral nerve blocks, sciatic nerve blocks are infrequently used. The expected area of anesthesia is limited, the techniques are frequently considered difficult, even "extremely difficult" (1), and a high incidence of complications is often anticipated.

In recent years, several reports have focused on the technical aspects or advantages of some of the blocking procedures of the sciatic nerve either proximally (2–6) or at the knee (7,8), but no overall assessment has been made and making comparisons between techniques remains difficult. This prompted us to design a prospective study of the three main approaches for blocking of the sciatic nerve aimed at evaluating their ease, safety, and reliability in children. The protocol study received institutional approval.

Material and Methods

Anatomical Considerations

The sciatic nerve is the largest nerve of the body. This mixed nerve derives from the sacral plexus and consists of two separate nerves, the tibial and common peroneal nerves, enclosed in a common sheath (however, in ~10% of patients, the two nerves are separately ensheathed). The sciatic nerve emerges from the pelvis through the sciatic foramen. It reaches the back of the thigh between the greater trochanter of the femur and the ischial tuberosity. It runs over the posterior aspect of the iliac bone and enters the subgluteal space below the piriformis muscle, accompanied by the posterior femoral cutaneous nerve, the inferior gluteal nerve, and several vessels. It then passes over the obturator internus, gemelli, obturator externus, and quadratus femoris muscles

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Table 1. Surgical Indications

Indications	Group P	Group L	Group A
Fractured shaft of the tibia and tibial osteotomies	7	13	16
Operations on ankle and foot	19	19	18
Club foot repair	4	3	6
Bimalleolar fractures	2	7	3
Osteotomies	13	9	9
Removal of implants (foot and leg)	11	3	4
Ingrowing toenails	14	10	10
Skin grafts and wound dressings	9	15	12
Total	60	60	60

before entering the thigh immediately posterior to the femur. It then runs toward the popliteal fossa, lying on the outer surface of the adductor magnus, within the posterior medial compartment of the thigh. This compartment is limited by the septum intermusculare femoralis mediale and a reinforcement of the posterior fascia of the adductor magnus muscle.

The posterior femoral cutaneous nerve (or posterior cutaneous nerve of the thigh) is a sensory nerve originating from the sacral plexus (ventral rami of S-1 to S-3 spinal nerves) and lying medial or posterior to the sciatic nerve (in a completely separate sheath). It enters the thigh deep to the fascia lata and runs toward the popliteal fossa, supplying sensory innervation to the dorsal aspect of the lower part of the gluteal area, the medial and posterior aspects of the thigh, and the popliteal fossa.

Material

One hundred eighty children, 67 female and 113 male, undergoing surgery of the leg, ankle, or foot (Table 1), were selected after informed consent had been obtained from parents and, whenever possible, from the patients themselves. The patients ranged in age from 3 mo to 18 yr and in weight from 5.5 to 79 kg. They were randomly allocated to one of three equal groups differing from one another in the technique used for blocking the sciatic nerve, i.e., posterior (group P), anterior (group A), and lateral (group L) approaches.

Methods

Anesthetic procedures. GENERAL ANESTHESIA. As usual in our pediatric unit (9,10), in most patients (173/180) the blocks were performed after induction of light general anesthesia that, preceded by 0.02 mg/kg atropine and 0.05–0.1 mg/kg diazepam, consisted of induction with either halothane (in 65%)

 $N_2O/35\%$ O_2) or intravenous thiopental (4 mg/kg) as preferred by the children, and maintenance with 0.25%-0.50% halothane in 65% $N_2O/35\%$ O_2 .

SELECTION OF MATERIALS. We used one of three 22-gauge insulated needles, 50, 100, and 150 mm long, depending on the depth to which the needle had to be inserted in children to reach the sciatic nerve using the different techniques (11). In all patients, anesthetized or not, we tried to locate the sciatic nerve by electrical stimulation using a nerve stimulator (Myotest from Datex) adjusted to deliver 2-mA impulses every second. If twitches were not elicited in muscles supplied by the sciatic nerve (i.e., below the knee) after three attempts, a loss-of-resistance technique was used as recommended by McNicol (3).

BLOCKING PROCEDURES. The posterior approach used in group P (60 patients) was that described by Winnie (1) (and derived from Labat's technique), with simplified landmarks. The patients were placed in the semiprone position, with the side to be operated lying uppermost, and the site of puncture was marked at midpoint of the line extending from the caudal end of the coccyx to the greater trochanter of the femur. The block needle was inserted at right angles to the skin (i.e., both medially and ventrally) pointing toward but just lateral to the ischial tuberosity until either twitches were elicited in muscles supplied by the sciatic nerve or loss of resistance was felt.

The block procedures performed in patients in groups L and A were similar to those described by Winnie (1) for the anterior approach and by Ichiyanigi (12) as modified by Guardini et al. (4) for the lateral approach. In both instances the patients were placed in the supine position, a nerve stimulator was used for locating the sciatic nerve, and when muscle twitches were not elicited after three attempts, a loss-of-resistance technique was used (3).

selection of local anesthetics. Four anesthetic solutions, each with 1:200,000 epinephrine, were used (15 patients in each group) depending on the expected duration of surgery, the necessity for intraoperative motor blockade, and the need for postoperative analgesia: (a) 1% lidocaine; (b) 0.5% bupivacaine; (c) a mixture of equal volumes of 0.5% bupivacaine and 1% lidocaine; and (d) a mixture of equal volumes of 0.5% bupivacaine and 1% etidocaine. The local anesthetic solution was administered on a weight basis: (a) 0.5 mL/kg in patients weighing less than 20 kg; and (b) 10 mL plus 0.25 mL/kg of patient's weight exceeding 20 kg, up to 25 mL maximum injected volumes.

Table 2. Success Rate and Adverse Effects

	Group P	Group L	Group A
Events	n (%)	n (%)	n (%)
Number of attempts			· · · · · · · · · · · · · · · · · · ·
1 attempt	53 (88)	47" (78)	37 ⁶ (62)
2 attempts	4 (7)	7 (12)	8 (13)
3 attempts	1 (2)	2 (3)	3 (5)
No twitches	2 (3)	4 (7)	12 (20)
Success rate			
Typical twitches	52 (87)	55 (92)	47° (78)
Sensory block	52 (100)	55 (100)	46 (98)
Atypical twitches	6 (10)	1 (2)	1 (2)
Sensory block	3 (50)	0 (0)	0 (0)
Air-detection	2 (3)	4 (7)	12 ^b (20)
Sensory block	0 (0)	3 (75)	7 (12)
Overall success rate	55 (92)	58 (97)	53 (89)
Adverse effects			
Traumatic puncture	0 (0)	0 (0)	3 (5)
Numbness	7 (12)	10 (17)	9 (15)
Neurological sequelae	0 (0)	0 (0)	0 (0)

Significant difference with both group P and group A. Significant difference with both group P and group L.

Monitoring procedures and evaluation of anesthesia. Electrocardiogram tracings, blood pressure, respiratory rate, and, in anesthetized patients, tidal volume and end-tidal CO₂ were monitored during the procedures. The block was considered successful when the scheduled operation was achieved without any additional treatment. Sensory block was evaluated after completion of surgery by sustained skin pinching. It was considered satisfactory when (a) the patient remained unaffected by repeated nociceptive stimuli applied to dermatomes supplied by the tibial and common popliteal nerves; and (b) when the patient felt skin pinching but not as an unpleasant stimulation or, in the youngest, reacted weakly to pinching in either or both dermatomes without attempting to withdraw the limb. In other instances the block was considered unsuccessful.

Motor blockade was tested by asking patients to move their ankles and toes or, in the youngest children, by applying stimuli aimed at eliciting withdrawal movements while immobilizing their thighs. Motor function was evaluated by comparing to the unblocked side and motor blockade was considered present when no or only weak and occasional movements of the ankle and toes were obtained after several stimuli, and absent when there was no difference in response between the anesthetized and the contralateral sides.

A recovery chart was filled in for each patient based on hourly evaluations until recovery was complete. Duration of sensory block was measured as the time between injection and the first evidence of pain (complaints of pain, crying, restlessness, or autonomic responses such as tachycardia, hypertension, and/or sweating in nonfebrile patients).

All patients were reexamined at a postoperative visit 5–16 days later. Delayed adverse effects and neurological impairment were carefully sought and, if present, recorded.

Statistical Methods

Results were expressed as mean \pm sp. They were compared using nonparametric Mann–Whitney test. Qualitative variables were evaluated using χ^2 test. Differences were considered statistically significant with P < 0.05.

Results

Success Rate and Number of Attempts

The use of a nerve stimulator aimed at eliciting twitches in muscles supplied by the sciatic nerve proved effective in 162 (90%) patients. The procedure was successful on the first attempt in 88% of patients in group P, in 78% in group L (significantly different from group P), and in 62% in group A (significantly different from both groups P and L).

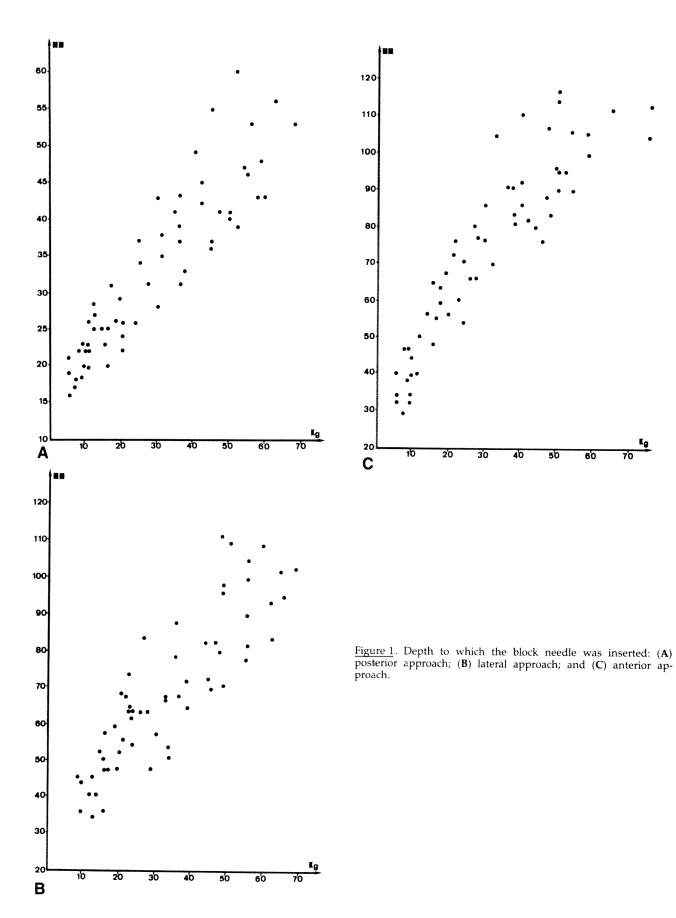
Twitches were "typical" in 154 patients, of whom 153 developed sciatic nerve block; they were atypical in eight patients, i.e., involving muscles not supplied by the sciatic nerve, e.g., gluteus muscles in group P and adductors in groups L and A. Only three of these eight patients developed sensory blockade in dermatomes supplied by the sciatic nerve.

Electrical stimulation was ineffective in producing motor responses in 18 patients, including 12 in group A (a significant difference as compared with either group). The loss-of-resistance technique was then used and sciatic nerve block developed in ten (56%) patients (this success rate was significantly less than that seen after typical muscle twitches were elicited).

The overall failure rate was 13 (7%) out of 180 procedures, almost equally distributed in the three groups (Table 2). Three vascular punctures, including one arterial, occurred, all in group A.

Depth at Which the Sciatic Nerve Was Located

The distance the needle was inserted at the time of injection is shown in Figure 10²; it correlated with patient's age and weight and was significantly less in group P than in either group L or group A (in the latter two groups, this distance was almost the same).





<u>Figure 2</u>. Spread of the anesthetic solution (data from patients not included in this study): (A) posterior approach; (B) lateral approach; and (C) anterior approach.



Spread of the Anesthetic Solution and Distribution of Anesthesia

The spread of the anesthetic solution with the three techniques is shown in Figure 2. Although it was different in the three groups, it resulted in the same anesthetized area in the lower limb when the block was successful (Table 3): the dermatomes supplied by the tibial and common peroneal nerves were equally

P. 24, 549

Table 3. Distribution of Anesthesia

	Sensory (motor) block			
Dermatomes (myotomes) supplied	Group P	Group L	Group A	
Tibial nerve	55 (43)	58 (54)	54 (49)	
Peroneal nerve	55	58	54	
Posterior femoral cutaneous nerve	53°	56 ^a	51 ^a	
Block of lumbar plexus nerves	0 (0%)	0 (0%)	0 (0%)	

[&]quot;The posterior femoral cutaneous nerve is a sensory nerve.

anesthetized in the 167 successful blocks, and, in addition, dermatomes supplied by the posterior femoral cutaneous nerve were blocked in 161 patients (96%) with no statistical difference as to local anesthetic administered. A motor block developed in 147 patients (88% of successful blocks), significantly less often in group P than in either group A or group L. The four anesthetic solutions resulted in the same frequency of motor blockade except in group P patients given either 0.5% bupivacaine or a mix of lidocaine and bupivacaine (P < 0.05).

Duration of the Block

Sensory blockade lasted significantly longer than motor blockade with all anesthetic solutions, but no significant differences in the duration of either the motor block or the sensory block were observed in the three groups when the same local anesthetic was used (Table 4).

Adverse Effects and Sequelae

Twenty-six patients mentioned numbness in the relevant lower limb during recovery from the block. No delayed adverse effect or complication occurred and recovery from both motor and sensory blockade was complete in all patients.

Discussion

Sciatic nerve block using electrical stimulation is a reliable technique; our overall success rate exceeded 90% of procedures. However, the three approaches were not equally easy: the nerve was located on the first attempt in almost 90% of patients using the posterior route, whereas the anterior route was technically more difficult and led to several vascular penetrations. When typical muscle twitches were elicited, the success rate was close to 100%. Con-

versely, when the local anesthetic was injected while muscle twitches were atypical, the sciatic nerve usually remained unaffected. In the absence of motor response to electrical stimuli, the loss-of-resistance technique failed in one-third of patients; however, as the technique was used only when electrical stimulation had already been unsuccessful after three attempts, it cannot be concluded that the loss-of-resistance technique is less effective. In fact, the loss-of-resistance technique resulted in successful blocks in two-thirds (ten of 18) of patients in whom the sciatic nerve would probably not have been anesthetized if electrical stimulation only had been used

Although the spread of the anesthetic was different in the three groups due to the site of injection, the sensory block was equally distributed in dermatomes supplied by the tibial and common peroneal nerves (and their division branches). More surprisingly, the posterior femoral cutaneous nerve was anesthetized in most patients even though this nerve runs in a fascial compartment quite separate from that enclosing the sciatic nerve. This may be specific to children; Hughes and Brown, experimenting on themselves, found that their loss-of-resistance technique for posterior femoral cutaneous nerve block did not block their sciatic nerves (13). Spread of the anesthetic solution to the posterior femoral cutaneous nerve may be due to the loose attachment of perineural sheaths and fascia planes in children that usually allow an extensive spread of local anesthetics along nerve trunks after both central and peripheral nerve blocks (11). The same increase in spread of injected solution along fascial planes may explain why even superficial intragluteal injections, i.e., at a considerable distance from the sciatic nerve, can result in severe damage of this nerve if a neurotoxic drug is administered, as reported several years ago (14-16), thus contraindicating intragluteal injections, at least in infants, even when direct nerve trauma is virtually impossible.

No delayed complications or neurological sequelae were observed, even in group P (intragluteal approach), thus confirming the safety of these blocking procedures and the absence of deleterious effects of local anesthetics on the sciatic nerve (2–5,17).

Whatever the local anesthetic injected, the sensory block lasted longer than usually expected after administration of other nerve blocks. Also, motor blockade frequently occurred even when low concentrations of local anesthetics were given (final concentration of the lidocaine-bupivacaine mixture was 0.5% lidocaine and 0.25% bupivacaine). The reasons for such an apparent sensitivity of the sciatic nerve to

	Table 4. Duration of	of Sensory and Motor	r Blockade According	to the Local	Anesthetic Administere	ed
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	Group P		Group L		Group A	
Type of block	Patients (n)	Duration ^a (h)	Patients (n)	Duration* (h)	Patients (n)	Duration* (h)
Sensory block						
Lidocaine	13	5.5 ± 1.6	15	6.1 ± 1.4	13	6.0 ± 2.0
Bupivacaine	15	8.0 ± 2.2	14	8.1 ± 0.9	14	8.3 ± 2.1
Bupivacaine + lidocaine	13	6.7 ± 1.7	14	7.1 ± 1.1	13	7.5 ± 1.4
Bupivacaine + etidocaine	14	8.2 ± 0.5	15	8.2 ± 1.6	14	8.4 ± 2.5
Motor block						
Lidocaine	12	3.3 ± 1.2	15	3.1 ± 0.9	12	3.5 ± 1.4
Bupivacaine	10	4.7 ± 0.8	14	4.8 ± 0.6	14	4.4 ± 1.2
Bupivacaine + lidocaine	7	3.7 ± 1.1	11	3.9 ± 1.5	11	4.3 ± 1.6
Bupivacaine + etidocaine	14	5.6 ± 2.1	14	6.0 ± 1.6	13	5.4 ± 2.3

[&]quot;Mean ± sp.

local anesthetics are not established. In the youngest patients, incomplete myelinization of nerve fibers may favor the contact of the local anesthetic with motor fibers. Also, muscle strength is weaker (thus easier to impair) in myotomes supplied by the sciatic nerve than in those supplied by the femoral nerve. However, such factors probably cannot play a significant role in older children and adolescents, and further studies would be necessary to evaluate this peculiarity.

The slight difference regarding motor blockade between group P, on the one hand, and groups L and A, on the other, may be related to the size of the sciatic nerve at the site of injection: the nerve is larger (thus more difficult to block) at the level of the ischial tuberosity (group P) than it is close to the femoral diaphysis (groups L and A).

In conclusion, the most suitable techniques for blocking the sciatic nerve proximally are via either the posterior (which remains the easiest approach) or the lateral route, which is of special value when the patient cannot be placed in the lateral position (extensive wounds, unstable fractures of the limb). The use of a nerve stimulator delivering 2-mA impulses every second provides an invaluable help in locating the sciatic nerve, as virtually 100% good results can be expected when typical twitches are elicited in muscles supplied by this nerve, despite the great depth to which the needle must be inserted.

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Effects of Sufentanil on Cerebral Circulation and Metabolism in Dogs

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MILDE LN, MILDE JH, GALLAGHER WJ. Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg 1990;70:138–46.

The cerebral and peripheral vascular effects of sufentanil (10–200 $\mu g/kg$) were examined in dogs. The cerebral blood flow (CBF) was measured continuously by an electromagnetic flow probe on the outflow of the posterior sagittal sinus. Sufentanil at all doses significantly increased CBF that lasted for ~20 min. The CBF then gradually decreased so that it was significantly below baseline levels by the end of the 60-min study period. The transient increase in CBF was accompanied by an equally transient statistically significant decrease in cerebrovascular resistance. Intracranial pressure did not change. Sufentanil produced an electroencephalographic pattern of deep anesthesia accompanied by a

decrease in cerebral oxygen consumption significantly below baseline levels. At the end of the study tissue concentrations of metabolites taken from the cerebral hemispheres were within normal limits, indicative of a normal cerebral energy state. Sufentanil had little effect on systemic hemodynamics. The observation that sufentanil significantly increases CBF in the absence of seizure activity makes it unique among the narcotics. It is hypothesized that in the presence of decreased intracranial compliance, this sudden increase in CBF, although transient, may be detrimental if it is accompanied by an acute increase in intracranial pressure which could produce cerebral ischemia.

Key Words: ANESTHETICS, INTRAVENOUS—sufentanil, fentanyl. BRAIN, BLOOD FLOW.

Sufentanil is a potent synthetic opioid analgesic (1) developed for use as a total intravenous anesthetic for major surgical procedures (2). Sufentanil produces hypnosis and analgesia without the use of additional anesthetic agents. Sufentanil, 5–12 times more potent than fentanyl (1,3), has a significantly higher therapeutic index than fentanyl (1,4). It has been reported that, after sufentanil analgesia, patients are more rapidly awake and lucid than those receiving fentanyl analgesia (3), and that postoperative analgesia is greater and respiratory depression less than in patients recovering from fentanyl-nitrous oxide (N₂O) anesthesia (5). Hemodynamic changes during sufentanil anesthesia are reported to be minimal. In patients undergoing noncardiac (6) or cardiac surgery (7,8) there is not only little or no change in arterial

blood pressure, cardiac output, or peripheral vascular resistance, but also a favorable myocardial oxygen balance. Sufentanil, like fentanyl, reduces endocrine and metabolic responses to surgical stress (5,9). Sufentanil can produce deep levels of anesthesia as demonstrated by electroencephalographic (EEG) changes to high-amplitude slow waves or burst suppression (10,11) with doses as low as 2.5 μ g/kg in humans (12).

Because of the above characteristics, sufentanil has been advocated for use during neurosurgical procedures. Two clinical studies have reported the use of a bolus dose (2–20 μ g/kg) of sufentanil as the major anesthetic for craniotomy (13,14). Both reported cardiovascular hemodynamic stability and rapid awakening; neither measured the cerebral hemodynamic or metabolic effects of sufentanil.

However, the cerebral hemodynamic and metabolic effects of an anesthetic should be known before that anesthetic is advocated for neurosurgery. Only one study, in rats, has reported the cerebral effects of sufentanil (15). The purpose of the present study was to determine the effects of a large dose range of sufentanil on cerebral function, cerebral blood flow (CBF), intracranial pressure (ICP), cerebral oxygen

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consumption (CMRo₂), and the resultant cerebral energy state as well as systemic hemodynamics in dogs.

Methods

Upon approval of the Animal Care and Use Committee and the Research Committee of the Mayo Clinic, anesthesia was induced in 18 adult fasting mongrel dogs with high concentrations of halothane in oxygen administered in an airtight box. The animals were intubated and anesthesia was maintained for the surgical preparation with 1 minimum alveolar concentration (MAC) halothane (0.9% end-tidal), 60%-70% N₂O, balance oxygen, adjusted to maintain Pao₂ = 150 ± 10 (se) mm Hg. The animals were paralyzed with pancuronium (0.1 mg/kg) and mechanically ventilated to maintain normocarbia (Paco₂ = 40 ± 2 mm Hg). Thereafter, ventilation was not further adjusted. Cannulas were placed via cutdown into a femoral artery for blood sampling and measurement of mean arterial pressure (MAP), into a femoral vein, and percutaneously into two peripheral veins for drug and fluid administration (normal saline at 75 mL/h). A 5F Swan-Ganz catheter was floated into a pulmonary artery from a cutdown of the right external jugular vein for measurement of right atrial (RAP), pulmonary arterial, and pulmonary capillary wedge pressures, blood sampling, measurement of body temperature, and measurement of cardiac output by thermodilution. Brain temperature, monitored with a parietal epidural thermistor, was maintained near 37°C with heating pads and lamps as necessary. Intracranial pressure was measured with an epidural fiberoptic device (model P-1500, Ladd Research Industries, Burlington, Vt.). The electrocardiogram was recorded continuously from limb leads. To determine depth of anesthesia a four-lead EEG was recorded from bifrontal and biparietal disk electrodes cemented to the skull to minimize artifact.

After the administration of 300–400 U/kg heparin, the sagittal sinus was exposed, isolated, and cannulated as previously described (16) for direct continuous measurement of CBF by a square-wave electromagnetic flow meter (17). The sagittal sinus drains primarily the anterior, superior, and lateral portions of the cerebral hemispheres, i.e., $\sim 54\%$ of the total brain weight (18). This sagittal sinus blood flow is diverted to a reservoir from which it is returned via a roller pump to the animal through the femoral vein cannula.

Blood oxygen contents were calculated from measurement of oxyhemoglobin concentration and oxy-

gen tension. Blood glucose and lactate concentrations were measured using a membrane-bound enzyme (glucose oxidase or lactate oxidase) technique (model 23A, Yellow Springs Instrument Co., Yellow Springs, Ohio). Cerebral metabolic rate for oxygen was calculated as the product of CBF and the arterial-sagittal sinus blood oxygen content difference; whole-body oxygen consumption was calculated as the product of cardiac index (cardiac output expressed as liters per minute per square meter) and the arterial-mixed venous oxygen content difference. Cerebral vascular resistance index was calculated as the quotient of cerebral perfusion pressure (the difference between MAP at the head level and ICP) and CBF; systemic vascular resistance index was calculated as the quotient of MAP – RAP and cardiac index.

Continuous monitoring included MAP, RAP, pulmonary arterial pressure, EEG, ECG, temperature, CBF, and ICP. Intermittent measurements included arterial, mixed venous and sagittal sinus blood gas tensions and pH, hemoglobin and oxygen saturation for calculation of CMRo₂ (measured every 5 min), blood glucose and lactate (measured every 15 min), serum catecholamines (measured every 30 min), plasma sufentanil levels (measured every 10 min), and end-tidal halothane, N₂O, and CO₂ concentrations measured by mass spectrometry.

When the surgical preparation was completed, skin and muscle infiltration with 0.25% bupivacaine was made around all incisions. The halothane was decreased to an end-tidal concentration of <0.1%. Once this was achieved, nitrogen (N_2) was substituted for N_2 O. To maintain a hemodynamic steady state during the period of baseline measurement, each animal's eyes were covered and ears plugged with cotton to decrease outside stimulation and no further manipulation of the animal was done. When the end-tidal N_2 O was <10 mm Hg, baseline measurements were obtained in triplicate for 15–20 min.

After this, sufentanil was given as a bolus dose of $10 \ (n=1)$, $20 \ (n=3)$, $50 \ (n=2)$, $80 \ (n=1)$, $100 \ (n=2)$, $150 \ (n=2)$, or $200 \ (n=2) \ \mu g/kg$. Each animal received only one dose of sufentanil and cerebral and systemic hemodynamic function and metabolism were then measured for $60 \ \text{min}$ after this administration

At the end of the study, the dura mater was exposed and incised and simultaneous bilateral cortical biopsies were made by a technique that deposits a sample of brain (200–400 mg) immediately into liquid nitrogen (19). The tissue was prepared for analysis (20) and tissue extracts were analyzed by enzymatic fluorometric techniques for phosphocreatine, glucose, and lactate (21). The energy charge of

the brain tissue was expressed as ([ATP] + 0.5[ADP])/([ATP] + [ADP] + [AMP]) (22).

For the determination of plasma sufentanil concentration, sufentanil and the internal standard alfentanil were analyzed by a modification of the methods of Phipps et al. (23) and Van Rooy (24). Plasma samples were stored at -70°C until extracted. Before use, glassware was exposed to a 5% solution of dimethyldichlorosilane (Eastman Kodak Co., Rochester, N.Y.) in toluene and then rinsed in toluene. After thawing, to each 1.0 mL of plasma was added 0.1 mL of aqueous alfentanil HCl (0.5 μ g/mL), 0.1 mL 4 M NaOH, and 5.0 mL 99% mole pure benzene (Fisher Scientific Co., Pittsburgh, Pa.) in a 13 × 100-mm screw-top culture tube with a polytetrafluorethylenelined cap. The contents were mixed on a rotary mixer for 10 min and then centrifuged for 20 min at 900 g. The upper benzene layer (4.5 mL) was transferred to a 12-mL conical graduated centrifuge tube. The contents were evaporated to dryness at 40°C with N2. The residue was reconstituted with 50 μ L of benzene and 5 µL was injected onto the gas chromatograph column. A gas chromatograph (model 5880 A, Hewlett-Packard Co., Palo Alto, Calif.) equipped with an N2 nitrogen phosphorus detector and an SPB-1 (30 M imes 0.75-mm ID, Supelco, Inc., Bellefonte, Pa.) column was used. The injector temperature was 300°C, column oven 260°C, and detector temperature 300°C. The carrier gas was chromatographic-grade helium flowing at 15 mL/min. Values for sufentanil were calculated using the ratio of the sufentanil peak areas to the alfentanil internal standard peak areas and read from a standard curve formed by the ratio of known standard sufentanil peaks to known standard alfentanil peaks. Stock standard solutions of sufentanil and alfentanil were prepared in methanol. Working standard solutions of sufentanil and alfentanil were prepared from stock standard solutions diluted with benzene in amounts comparable to the 20-fold concentration range of sufentanil in the canine plasma.

Results were analyzed for statistical significance of differences between each sufentanil dose by multiple analysis of variance. When no significant differences were found, the values obtained with all sufentanil doses were combined and the mean value determined. To eliminate the possibility of a type II statistical error (i.e., to conclude that there were no differences in values obtained at each dose of sufentanil when differences did exist) a power analysis was done. The power of detecting a 5% difference between values was 0.90 or greater. The mean values after the administration of sufentanil were compared to baseline values by analysis of variance and the

significance of differences tested by Student's *t*-test for paired data. Tissue concentrations of cerebral metabolites obtained at the end of the study were compared with normal canine values for our laboratory (25) by Student's *t*-test for unpaired data.

Results

Because no significant differences were found among the cerebral hemodynamic and metabolic values obtained after each sufentanil dose, the values obtained at each time interval for all doses of sufentanil were meaned. The means for the cerebral hemodynamic and metabolic values are presented in Table 1. Sufentanil produced a sudden larger increase in CBF which peaked at 2-5 min. Figure 1 shows the percentage change in CBF from baseline levels (83 \pm 6 $mL \cdot min^{-1} \cdot 100 g^{-1}$) with time. At 2 min CBF was 119 \pm 11 mL·min⁻¹·100 g⁻¹, a significant increase of 40% ± 8% above the baseline value. It remained significantly increased for 20 min. Thereafter, CBF gradually decreased back toward baseline levels. During the last 10 min of the study, CBF was significantly below baseline values. The transient increase in CBF was accompanied by a significant decrease in cerebrovascular resistance (Table 1). There was no significant change in ICP (Table 1).

Unlike its effect on the cerebral hemodynamic values, sufentanil produced a dose-related effect on cerebral function as manifested by changes on the four-lead EEG. Animals given 10– $50~\mu g/kg$ sufentanil developed high-amplitude slow waves lasting from 20 min to the full length of the study (60 min). Because of variation among dogs, the duration of the observed EEG effect was not related to dose within this dose range of 10– $50~\mu g/kg$. Animals given 100– $200~\mu g/kg$ had high-amplitude slow waves on the EEG that lasted throughout the study period. None of the animals demonstrated either a spike and wave pattern or a seizure pattern, both of which have been reported in rats (15) and humans (11).

The changes in cerebral function were accompanied by parallel changes in CMRo₂ (Table 1 and Figure 2). After a transient increase in CMRo₂ at 2 min, CMRo₂ gradually decreased and was significantly below baseline levels for the last 25 min of the study. There was no dose-related effect of sufentanil on CMRo₂. For example, 10 min after administration of sufentanil when the EEG demonstrated a decrease in cerebral function on EEG, there was no difference in CMRo₂ between dogs given 10–50 μ g/kg (CMRo₂ = 4.07 \pm 0.16 mL·min⁻¹·100 g⁻¹), and those given 100–200 μ g/kg (CMRo₂ = 3.99 \pm 0.20 mL·min⁻¹·100 g⁻¹).

Table 1. Cerebral Hemodynamic and Metabolic Values Before and After Sufentanil

Time (min)	CBF (mL·min ⁻¹ ·100 g ⁻¹)	$CMRo_2$ (mL·min ⁻¹ ·100 g ⁻¹)	ICP (mm Hg)	CVRI (mm Hg·mL ⁻¹ ·min ⁻¹ ·100 g ⁻¹)
Baseline	83 ± 6	4.05 ± 0.12	3 ± 1	1.46 ± 0.12
Sufentanil				
2	119 ± 11°	4.51 ± 0.33^{4}	3 ± 1	1.18 ± 0.15
5	107 ± 10°	4.13 ± 0.10	5 ± 1	1.24 ± 0.13
10	100 ± 9^{a}	4.01 ± 0.11	4 ± 1	$1.28 \pm 0.11^{\circ}$
15	97 ± 9"	3.92 ± 0.11	4 ± 1	$1.23 \pm 0.10^{\circ}$
20	94 ± 4	3.89 ± 0.10	4 ± 1	$1.18 \pm 0.09^{\circ}$
25	91 ± 8	3.86 ± 0.09	4 ± 1	$1.22 \pm 0.10^{\circ}$
30	90 ± 8	3.81 ± 0.11	4 ± 1	$1.24 \pm 0.10^{\circ}$
35	85 ± 7	$3.76 \pm 0.11^{\circ}$	4 ± 1	$1.27 \pm 0.11^{*}$
40	80 ± 6	$3.81 \pm 0.13^{\circ}$	4 ± 1	1.30 ± 0.11
45	75 ± 6	$3.74 \pm 0.14^{\circ}$	4 ± 1	1.35 ± 0.12
50	72 ± 6	$3.64 \pm 0.15^{\circ}$	4 ± 1	1.37 ± 0.13
55	72 ± 6°	$3.66 \pm 0.11^{\circ}$	4 ± 1	1.33 ± 0.12
60	74 ± 6°	$3.66 \pm 0.12^{\circ}$	5 ± 2	1.25 ± 0.11

CBF, cerebral blood flow; CMRo₂, cerebral metabolic rate for oxygen; ICP, intracranial pressure; CVRI, cerebrovascular resistance defined as an index per 100 g brain tissue.

Because no significant differences were found among the cerebral hemodynamic and metabolic values obtained after each sufentanil dose, the values obtained at each time interval for all doses of sufentanil were meaned. The above values are these means \pm sg. "Significantly different from baseline (P < 0.05).

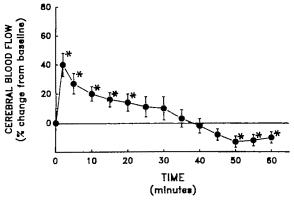
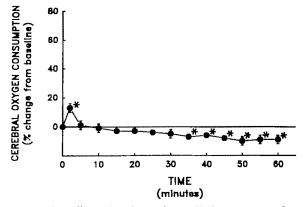


Figure 1. The effect of sufentanil on CBF expressed as a percentage change from the baseline value. Sufentanil produced a significant increase in CBF which lasted 20 min followed by a gradual decrease in CBF with time. Values are expressed as mean \pm se. Asterisks denote a significant change from baseline value.

Sufentanil had no significant effect on systemic hemodynamics (Table 2 and Figure 3). There was no significant change in MAP immediately after the administration of sufentanil, although MAP decreased gradually throughout the study until it was significantly below baseline levels at 60 min.

The effects of sufentanil on blood gas tensions and chemistries are summarized in Table 3. The administration of sufentanil had no effect on arterial oxygen and carbon dioxide tensions. It did produce a significant decrease in arterial pH which worsened throughout the study period. This was accompanied by an increase in blood lactate. Sufentanil also significantly increased blood glucose levels. Norepinephrine levels 30 and 60 min after administration of



<u>Figure 2</u>. The effect of sufentanil on CMRo₂, expressed as a percentage change from baseline. After an initial transient (2 min) increase, there was a gradual but significant decrease in CMRo₂ with time. Values are expressed as mean \pm se. Asterisks denote a significant change from baseline values.

sufentanil tended to be increased over baseline levels but not significantly so because of the wide individual variation.

Blood levels of sufentanil as a function of time are presented in Figure 4. There was the expected correlation between sufentanil dose and blood level. There was no correlation between peak blood levels and change in CBF. There are missing data points for the 10-µg/kg dose because the plasma sufentanil concentrations were below the limits of the assay.

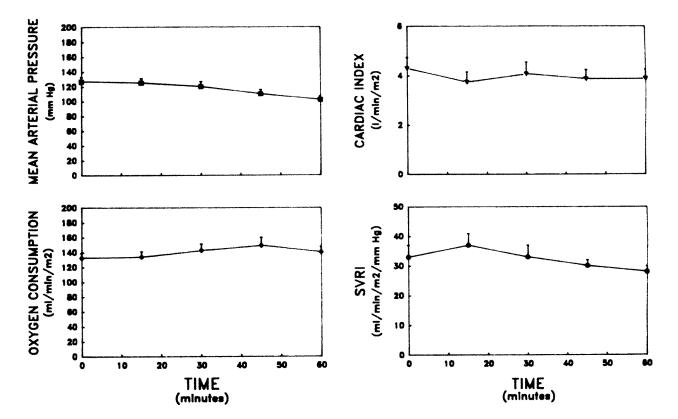
The concentrations of cerebral metabolites in tissue obtained at the end of the study (Table 4) were within normal limits, normal levels of the high-energy metabolites, ATP and phosphocreatine, without any accumulation of lactate. This indicates that there were

Table 2. Systemic Hemodynamic Values Before and After Sufentanil

Time (min)	MAP (mm Hg)	HR (beats/min)	RAP (mm Hg)	PCWP (mm Hg)	CI $(L \cdot min^{-1} \cdot m^{-2})$	SVRI (mm Hg·L ⁻¹ ·min ⁻¹ ·m ⁻²)	Ýo ₂ (mL·min ⁻¹ ·m ⁻²)
Baseline	127 ± 6	117 ± 8	3 ± 1	6 ± 1	4.3 ± 0.5	33 ± 4	132 ± 7
Sufentanil 15	125 ± 6	99 ± 10	4 ± 1	6 ± 1	3.7 ± 0.4	37 ± 4	134 ± 7
30	120 ± 7	99 ± 10	3 ± 1	6 ± 1	4.1 ± 0.5	33 ± 4	143 ± 9
45 60	110 ± 6 102 ± 5^a	98 ± 9 98 ± 11	4 ± 1 4 ± 1	5 ± 1 5 ± 2	3.9 ± 0.4 3.9 ± 0.4	30 ± 2 28 ± 2	149 ± 11 140 ± 7

MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac output calculated as an index per square meter body surface area; SVRI, system vascular resistance calculated as an index; $\hat{V}o_2$, total body oxygen consumption.

[&]quot;Significantly different from baseline (P < 0.05).



no detrimental effects of sufentanil on the energy state of the brain.

In three additional dogs the background respiratory gases were 70% NO_2 - O_2 rather than N_2 - O_2 during the baseline state and after the administration of 20, 50, or 150 μ g/kg sufentanil. A comparison of CBF under these conditions with the CBF measured under N_2 - O_2 ventilation is presented in Figure 5. Under N_2 O- O_2 , the CBF in the baseline state was 206 \pm 36 mL·min⁻¹·100 g⁻¹, significantly higher than the CBF under N_2 - O_2 ventilation (83 \pm 6 mL·min⁻¹·100 g⁻¹). The administration of sufentanil significantly decreased CBF from the baseline measurements in the animals ventilated with N_2 O- O_2 . However, after the administration of sufentanil, CBF in the dogs

<u>Figure 3</u>. Sufentanil had no significant effect on MAP, cardiac index, whole-body oxygen consumption, or systemic vascular resistance index (SVRI). Values are expressed as mean \pm se.

receiving N_2O was not significantly different from CBF in the group ventilated with N_2 - O_2 . It was only during the baseline state that there was a difference.

Discussion

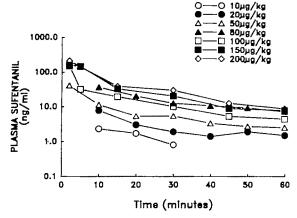
A large range of sufentanil doses was used in the present study. Recommended doses of sufentanil for patients undergoing surgery range from 1 to 30 μ g/kg. However, sufentanil alone, at the lower doses

Table 3. Blood Gas Tensions, pH, and Chemistries Before and After Sufentanil

					Catecholamines			
Time (min)	Pao ₂ (mm Hg)	Paco ₂ (mm Hg)	pН	Glucose (mg/dL)	Lactate (μm/mL)	Norepinephrine (ng/mL)	Epinephrine (ng/mL)	Total
Baseline	160 ± 3	41 ± 1	7.34 ± 0.01	114 ± 8	2.14 ± 0.26	0.46 ± 0.06	2.78 ± 0.82	3.24 ± 0.87
Sufentanil								
15	156 ± 4	43 ± 1	7.29 ± 0.01*	141 ± 13*	2.66 ± 0.26			
30	156 ± 5	43 ± 1	$7.29 \pm 0.01^{\circ}$	140 ± 10°	$2.57 \pm 0.20^{\circ}$	0.92 ± 0.40	2.99 ± 0.66	3.91 ± 0.77
4 5	156 ± 5	43 ± 1	7.28 ± 0.01^a	144 ± 12"	2.42 ± 0.21			
60	155 ± 5	43 ± 2	7.27 ± 0.01^{4}	138 ± 12	2.24 ± 0.21	1.07 ± 0.68	1.84 ± 0.31	2.91 ± 0.77

Mean ± se.

^{*}Significantly different from baseline value (P < 0.05).



<u>Figure 4</u>. Plasma sufentanil concentration over time after the administration of sufentanil. Values are the means for each sufentanil dose given ($10-200~\mu g/kg$). Because only one to three animals received each dose, no standard errors are given.

<u>Table 4</u>. Effect of Sufentanil on Concentrations of Cerebral Metabolites

	ATP (µmol/g)	EC	PCr (µmol/g)	Lactate (µmol/g)	
Sufentanil	2.00 ± 0.05	0.98 ± 0.01	3.09 ± 0.14		
Normal*	2.01 ± 0.01	0.87 ± 0.001	2.99 ± 0.12		

ATP, adenosine triphosphate; EC, energy charge; PCr, phosphocreatine. Normal canine brain metabolites described in Newberg et al. (25).

of 1–8 $\mu g/kg$, does not provide total anesthesia and must be used in conjunction with N₂O and/or sedative-hypnotic medication. Pilot studies in our canine model demonstrated that doses of 2 and 5 $\mu g/kg$ sufentanil alone did not produce deep anesthesia in the dogs (depth of anesthesia being measured by the EEG) for the time period of the study and these doses were not used. It has been reported that the EEG does reflect the depth of anesthesia with high-dose narcotics (10). The larger doses of sufentanil were used in an attempt to determine whether sufentanil alone could suppress electrical cortical activity to achieve an isoelectric EEG and to correlate any EEG

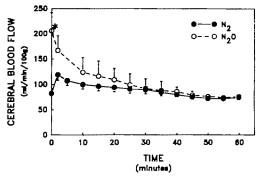


Figure 5. The effect of sufentanil on CBF with N_2O - O_2 ventilation (\bigcirc) or N_2 - O_2 ventilation (\bigcirc) . There is a significant difference in the baseline CBF values under N_2O or N_2 ventilation (at time 0) but no difference in CBF after the administration of sufentanil.

suppression with cerebral metabolism as has been done for other anesthetics. However, sufentanil in the doses studied (10–200 μ g/kg) produced only high-amplitude slow waves indicative of a moderate depth of anesthesia but did not produce either burst suppression or isoelectricity on the EEG. These EEG findings are similar to those reported for patients in which 15 μ g/kg sufentanil alone produced high-voltage slow delta waves (11).

The observation that sufentanil produces a significant increase in CBF lasting ~20 min is unique among the narcotics. It has been reported that in animals morphine (18), fentanyl (26-28), and sufentanil (15) decrease CBF. However, in all these studies the baseline condition to which the effect of the narcotic was compared included ventilation with N_2O . The effects of N_2O on CBF and metabolism vary with different species. These differences may be due to differences in sensitivity to N₂O among species. Nitrous oxide produces the greatest increase in CBF and metabolism in dogs (29-31). There could be two reasons why a narcotic would seem to decrease CBF if the control or baseline state were under N₂O analgesia. First, if N₂O were used in the baseline state, the addition of narcotic could provide enough analgesia and/or sedation to offset the hypermetabolism and increased CBF produced by the N₂O. In the study by Michenfelder and Theye (28), the administration of fentanyl to dogs ventilated with N2O produced a significant decrease in CBF and CMRo2, both of which returned by 20 min toward the baseline values obtained during N₂O-O₂ ventilation, the approximate alpha half-life of fentanyl (32). In other studies the control state with N₂O was achieved in groups of animals different from those given the narcotic so that the animals receiving narcotic never received N₂O. This was the experimental condition for two studies done in rats reporting the effects of fentanyl (27) and sufentanil (15). In these studies, control animals were ventilated with N2O throughout the study period. Animals receiving narcotics were initially ventilated with N2O but this was replaced with N_2 after administration of the narcotic. The CBF in the narcotic group was not measured until after the elimination of N₂O.

However, if baseline conditions were without N_2O , either morphine (33–35) or fentanyl (36,37) had no effect on CBF or fentanyl (38,39) increased CBF. In the latter two studies, fentanyl induced seizures which increased cerebral metabolism with an accompanying increase in CBF. Therefore, the interpretation of the results in the studies on the cerebral effects of narcotics in which N2O was used in the control or baseline state might have been that N₂O increased CBF in the control or baseline state rather than that the narcotics had a depressant effect on CBF. This is demonstrated by Figure 5 which depicts the effect of sufentanil on CBF when the background ventilation was N_2O-O_2 (open circles) or N_2-O_2 (closed circles). Because of the very high baseline CBF during N_2O - O_2 ventilation (206 \pm 36 mL·min⁻¹·100 g⁻¹), it appears that sufentanil significantly decreased CBF. However, the CBF values after the administration of sufentanil were the same despite the different background gases (N₂O vs N₂). This demonstrates that the significantly different baseline CBF values could influence the interpretation of the results of other studies.

Nevertheless, the observation of the present study that sufentanil alone significantly increased CBF in the absence of seizure activity makes it unique among the narcotics. Because it is an immediate and transient event, a continuous measurement of CBF must be used to observe it. Figure 6 is a CBF tracing from one animal that demonstrates the immediate change in CBF produced by sufentanil (200 μ g/kg). The interval of 20 min between the administration of sufentanil and the measurement of CBF in the study by Keykhah et al. (15) would have missed this event.

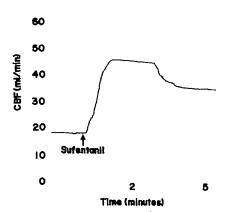


Figure 6. The continuous tracing of CBF from one animal demonstrating the immediate change in CBF after the administration of 200 μg/kg sufentanil.

The cause of this increase in CBF is unknown. There were no significant decreases in Pao2 or increases in Paco₂. There were no signs of cerebral stimulation on the EEG. Instead the EEG showed a pattern of deep anesthesia. Although the significant increase in CMRo₂ that was observed 2 min after the administration of sufentanil might indicate regional cortical seizure activity not observed with the four-lead EEG, this single value is more likely a function of an unsteady state due to the rapidly changing CBF. There was no significant increase in serum catecholamine levels although these were measured 30 and 60 min after the administration of sufentanil, so that a possible transient increase in serum catecholamine levels at the time of the increased CBF may have been missed. This seems unlikely as it has been reported that there is no change in serum catecholamines 1-5 min after the administration of sufentanil (40). Although sufentanil did produce a significant decrease in cerebral vascular resistance index in the dogs in the present study, sufentanil at doses of 1.5 μ g/kg (41) and 15 μ g/kg (42) does not cause histamine release in humans, so this seems an unlikely cause of the decrease in cerebral vascular resistance index.

The observed increase in CBF was not accompanied by any significant change in ICP, which at all times remained within normal limits. However, significant increases in ICP were not expected because the animals had normal intracranial contents with normal intracranial compliance. However, many neurosurgical patients have decreased intracranial compliance owing to space-occupying masses or increased cerebrospinal fluid volume. Many of these patients may have maximized the normal compensatory mechanisms for intracranial masses such that any increase in intracranial volume might result in increased intracranial pressure. Under these conditions, a sudden increase in CBF caused by the administration of sufentanil might severely increase ICP,

which could potentially result in cerebral ischemia and/or herniation of brain contents.

A recent clinical study supports this hypothesis (43). In patients undergoing elective excision of supratentorial tumors, the administration of 1 μ g/kg sufentanil produced a significant 89% \pm 31% increase in cerebrospinal fluid pressure and a significant 25% decrease in cerebral perfusion pressure within the 10-min observation period (43).

If the results of the present animal study can be extrapolated to humans, the increase in cerebrospinal fluid pressure observed in patients is due to a sudden increase in CBF caused by the sufentanil. Whether or not these cerebral hemodynamic changes produced by sufentanil may be detrimental to neurosurgical patients has yet to be determined.

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DIPRIVAŅ INJECTION propofol

FMIII SION FOR IV ADMINISTRATION

DESCRIPTION: DIPRIVAN* (propofol) Injection is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2.6-Diisopropylphenol and has a molecular weight of 178 27. The empirical and structural formulas are

Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The emulsion is isotonic and has a pH of 70-85. In addition to the active component, propofol, the formulation also contains sopbean oil (100 mg/mL), glycerol (22.5 mg/mL) and egg lecithin (12 mg/mL); with sodium hydroxide to adjust pH. CLINICAL PHARMACOLOGY: DIPRIVAN Injection is an intravenous hypnotic agent for use in the induction and maintenance of anesthesia. The pharmacokinetic profile of PRIVAN Injection can be characterized as follows: maintenance of anestriesia. The priarriacownetic profile of Dirrivivin Pigicion car be characterized as blowless. After a single rapid IV bolus dose, two distribution phases are seen, a rapid phase with a half-life of 1.8 to 8.3 min and a slower phase of 34 to 64 min. These distribution phases are associated with the movement of DIPRIVAN from highly perfused tissues (sees)-incl tissues) to less well-perfused tissues. The terminal elimination half-life of DIPRIVAN ranges from 300 to 700 min. With prolonged administration of DIPRIVAN Injection, the terminal elimination half-life may become extended beyond 700 min. DIPRIVAN has a high metabolic clearance that range in the properties of the eurmation nati-tier may become exteriore beyond 700 mill. Direntweet has a ringl interaction, clearance that argist from 1.6 L/min to 3.4 L/min in healthy 70 kg patients. This metabolic clearance exceeds estimates of hepatic blood flow, suggesting possible extrahepatic metabolism. DIPRIVAN has a large steady state distribution volume that ranges from 150 to 1,000 liters in healthy 70 kg patients. The long terminal elimination half-life of DIPRIVAN is due to the large steady state distribution volume which is presumed to be due to extensive drug partitioning

into tissues.

The termination of anesthetic drug effects of DIPRIVAN after a single IV bolus or a maintenance infusion is due to extensive redistribution from the CNS to other tissues and high metabolic clearance both of which will decrease blood concentrations. Recovery from anesthesia is rapid. Following induction (2.0 to 2.5 mg/kg DIPRIVAN Injection) and maintenance (0.1 to 0.2 mg/kg/min) of anesthesia for periods up to two hours, the majority of patients are generally awake, responsive to verbal commands, and oriented within 8 minutes. Recovery from the effects of DIPRIVAN Injection occurs due to metabolism and distribution during the first two exponents of the decay curve and is not dependent on the terminal elimination half-life. A study in six subjects showed approximately 70% of the administered radiolabeled DIPRIVAN injection dose was recovered in the urine in the

approximately 70% of the administered radiolabeled DIPRIVAN Injection dose was recovered in the urine in the first 24 hours and approximately 90% of the dose was recovered in the urine within five days. DIPRIVAN is chief metabolized by conjugation in the liver to inactive metabolites which are excreted by the kidney. A glicurronide conjugation metabolite accounted for about 50% of the administered dose. The exact metabolic fate of DIPRIVAN and the sites of possible "extrahepatic" metabolism have not been identified.

The pharmacokinetics of DIPRIVAN Injection do not appear to be altered by gender, chronic hepatic cirrhosis or chronic renal failure. The effects of acute hepatic or renal failure on the pharmacokinetics of DIPRIVAN have not been studied. With increasing age the clearance of DIPRIVAN decreases from a mean ± S.D. of 1.8 ± 0.4 L/min in young (18-35 years) patients. When given by an influsion for up to two hours, the pharmacokinetics of DIPRIVAN appear to be independent of dose (0.05-0.15 mg/kg/min) and similar to IV bolus pharmacokinetics. The steady state propofol blood concentrations are proportional to the rate of administration.

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics and narcotics) can

proportional to the rate of administration. Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics and narcotics) can increase the CNS depression induced by DIPRIVAN. Morphine premedication (0.15 mg/kg) with N₂O 67% has been shown to decrease the necessary DIPRIVAN Injection maintenance infusion rate and therapeutic blood concentrations, when compared to a nonnarcotic (lorazepam) premedication. An altentanil infusion rate of 50 mg/kg/h has been shown to replace the anesthetic effects of N₂O 67% and morphine premedication. Intravenous injection of a therapeutic dose of DIPRIVAN Injection produces hypnosis rapidly and smoothly intravenous injection of a therapeutic dose of DIPRIVAN Injection produces hypnosis rapidly and smoothly intravenous injection of a therapeutic dose of DIPRIVAN Injection produces hypnosis rapidly and smoothly intravenous injection of the produce of the

Intravenous injection of a therapeutic dose of DIPRIVAN Injection produces hypnosis rapidly and smoothly with minimal excitation, usually within 40 seconds from the start of an injection (one arm-brain circulation time). As with other rapidly acting intravenous anesthetic agents, the half-time of blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

Propotol blood concentrations required for maintenance of anesthesia have not been completely characterized. When nitrous oxide, oxygen, and propofol are used for maintenance of general anesthesia, supplementation with analgesic agents (eg. narcotics) is generally required; neuromuscular blocking agents may also be required. (See DOSAGE AND ADMINISTRATION.)

The hemodynamic effects of DIPRIVAN injection during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease).

is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease) with little or no change in heart rate and no appreciable decrease in cardiac output. If ventilation is assisted or

with rittle or no change in near rate and no appreciable decrease in cardiac output. In verniador is assisted controlled (positive pressure ventilation), the degree and incidence of decrease in cardiac output are accentuated. Addition of a potent opioid (eg. fentanyl) when used as a premedicant further decreases cardiac output. If anesthesia is continued by infusion of DIPRIVAN Injection, endotracheal intubation and surgical stimulation may return arterial pressure towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of DIPRIVAN during induction are generally more pronounced

studies have shown that the hemodynamic effects of DIPRIVAN during induction are generally more promotices than with traditional IV Induction agents. Insufficient data are available regarding the cardiovascular effects of DIPRIVAN Injection when used for induction and/or maintenance of anesthesia in elderly, hypotensive, debilitated patients, patients with severe cardiac disease (ejection fraction < 50%) or other ASA III/IV patients. However, limited information suggests that these patients may have more profound adverse cardiovascular responses. It is recommended that if DIPRIVAN Injection is used in these patients, a lower induction dose and a slower maintenance rate of administration of the drug be used. (See DOSAGE AND ADMINISTRATION.)

Clinical and preclinical studies suggest that DIPRIVAN Injection is rarely associated with elevation of plasma histamize levels and dose not cause signs of histamizine light reflease.

Clinical and precinitical studies suggest that other hand injection is fately associated with apnea. In 1573 patients with DIPRIVAN Injection is frequently associated with apnea. In 1573 patients who received DIPRIVAN Injection (2.0 to 2.5 mg/kg), apnea lasted 0-30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. During maintenance DIPRIVAN Injection (0.1 to 0.2 mg/kg/min) causes a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medications (eg., narcotics, containing a co

Clinical studies in humans and studies in animals show that DIPRIVAN Injection does not suppress th

response to ACTH.

Rreliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN Injection anesthesia produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic

Animal studies and limited experience in susceptible patients have not indicated any propensity of DIPRIVAN

Animal studies and initiate acceptance in society of the first process o

reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have

DIPRIVAN® (propotoi) Injection

not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.) CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity

to IPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because

compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known

Significance is not known.

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINIST RATION.) Patients should be continuously monitored for early signs of significant and/or bradycardia. Treatment may include increasing the rate of intra-enous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic

hyperlipemia, and pancratitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine In a many design of the solution). Venous sequelae (phiebits or thrombosis) have been reported rarely (< 19%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital forms used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animasis caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental

intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

which DIPRIVAN injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN injection unclear.

Drug Interactions: As DIPRIVAN injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg. atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg. succinylcholine) or surgical stimui.

The induction dose requirements of DIPRIVAN injection may be reduced in patients with intramuscular or intrampus premedication.

intravenous premedication, particularly with narcotics (eg. morphine, meperidine, and tentaryl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases

may increase the anesthetic effects of Der May Injection and may also sessim more photodices decreased in systolic, disastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of suplemental analgesic agents (eg. introus oxide or opioids). The concurrent administration of potent inhalational agents (eg. isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational anal agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of

the commonly used neuromuscular blocking agents (eg., succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been perfo

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propotol. Tests for mutagenicity included the Ames (using Salmonella sp) mutation test, gene mutation/gene conversion using Saccharomyces

included the Ames (using Salmonella sp) mutation test, gene mutation/gene conversion using Saccharomyces cerevisiae, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in threame tast at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. Pregnancy Category 8: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired trility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN injection is not recommended for obstetrics, including cesarean section deliveries. because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are

been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are

Padiatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and

effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow. Neurosurgical Anesinesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings. DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

Further studies are needed to substantiate what nappens to intracramia pressure rollowing DIPHIVAN injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent USC and and clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented

The following adverse events were reported in patients treated with DIPHIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1%—All events regardless of causality, derived from clinical trials.

Body as a Whole: Fever. Cardiovascular: Hypotension* (see also CLINICAL PHARMACOLOISY).

Hypertension. Central Nervous System: Movement. Headache. Dizziness, Twitching, Bucking/Jerking/

Thrashing, Clonic/Myoclonic Movement. Digestive: Nausea.** Vomiting.* Abdominal Cramping. Injection Site:

Burning/Stinging.** Pain.** Tinging/Numbness. Coidness. Respiratory: Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). Skin and Appendages: Flushing.

Incidence of unmarked events is 196-396; "396 to 1096; "*1096 or greater.

Incidence Less than 1% - Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *Italicized*.)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. Cardiovascular: Tachycardia

Permature Ventricular Contractions, Premature Arnal Contractions, Syncope, Abnormal ECG, ST Segment Depression. Central Nervous System: Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Patigue, Moaning, Rigidity. Digestive: Hypersali-vation, Dry Mouth, Swallowing. Injection Site: Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration.

Musculoskeletal: Myalgia. Respiratory: Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing. Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. Skin and Appendages: Rash, Urticaria. Special Senses: Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. Urogenital: Uring

Incidence Less than 11/e -- Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, Myocardial Ischemia. Central Nervous System: Arxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, Opisthotonus. Digestive: Diarrhea. Respiratory: Laryngospasm. Skin and Appendages: Diaphoresis. Pruritus, Conjunctival Hyperemia. Special Senses: Ear Pain, Nystagmus. Urogenital: Abnormal Urine. DRUG ABUSE AND DEPENDENCE: None known.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor

agents and/or anticholinergic agents.

The intravenous LD_{Sp} values are 53 mg/kg in mice and 42 mg/kg in rats.

The intravenous LD_{Sp} values are 53 mg/kg in mice and 42 mg/kg in rats.

The intravenous LD_{Sp} values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA fand I are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the

onset of anesthesia. It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 509k (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

of incremental injections

of incremental injections. When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%-50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

anesthetic and recovery profile. Influsion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DiPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DiPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia, such as atropine, DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. Adults: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	Variable rate infusion — titrated to the desired clinical effect. Adults: Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because

tis an emulsion. In clittled form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

— 5% Dextrose injection, USP

- Lactated Ringers Injection, USP
 Lactated Ringers and 5% Dextrose Injection

- Latitate Integris and 390 Dextrose injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection should be discarded at the end of the surgical procedure.

at the end of the surgical procedure.

HOW SUPPLIED: DIPRIVAN Injection (NDC 0038-0290) is available in ready-to-use 20-mL ampules containing

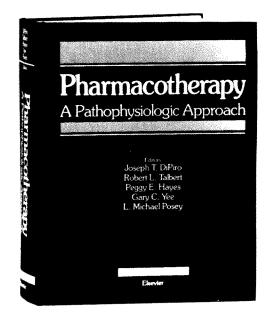
Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well belore use.

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For Information Contact:

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SMOOTH EMERGENCE GO HAND IN HAND

IN I.V. CONSCIOUS SEDATION

Rapid onset of sedation1

Minimal irritation and phlebitis after I.V. injection

 Only 1.29 percent (2/155) incidence of thrombophlebitis one week postprocedure with VERSED (midazolam HCI/Roche)²

Pronounced amnestic effect

 Minimal recall of the procedure – a majority of patients had little or no recall one hour postendoscopy.¹ Diminished recall is especially valuable when repeat procedures may be required.

Dosing Considerations

Because serious and life-threatening cardiorespiratory adverse events have been reported with VERSED, provide for monitoring, detection and correction of these reactions for every patient regardless of age or health status.

As a standard precaution, prior to I.V. administration, oxygen and resuscitative equipment should be immediately available and personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation should be ensured. I.V. VERSED should be titrated slowly; never give as a bolus. Respiratory depression and/or arrest may result from excess doses or rapid or single bolus. VERSED should be used as an induction agent only by persons trained in anesthesiology.

Reduce dosage in elderly or debilitated, in patients receiving narcotic premedication, and in those with limited pulmonary reserve. VERSED is 3 to 4 times as potent per mg as diazepam. Refer to the complete dosage and administration quidelines.

It is recommended that patients not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. Decision must be individualized.

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IN INDUCTION

Smooth emergence

 Patients treated with VERSED experience minimal anxiety and postoperative depression and rarely report any adverse emergence reactions.³

Better hemodynamic stability

 Less pronounced decreases in stroke volume, heart rate, cardiac output and systemic vascular resistance...and less pronounced increase in mean right atrial pressure compared to thiopental, although the differences were not statistically significant.¹



Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

Please see summary of product information on following page.

References: 1. Roche Scientific Summary: The Evaluation of VERSED® (brand of midazolam HCl/Roche) @, Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, New Jersey, 1986. 2. Phaosawasdi K, Rice P: SGA Journal:176-178, Spring, 1987. 3. White PF: Anesthesiology 57:279-284, 1982.

VERSED● (brand of midszotem HCl/Roche) (V MURCTION

Before prescribing, pieses consult complete product information, a summery of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzo-diazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy. WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent aliveay and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/aardisc arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VEFSED depresses respiration, and opicid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, agones, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VEFSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic. Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoda or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VEFSED and all other drugs should be evaluated before proceeding. Concomitant use of barbi

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of enesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more stowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with sge, reduce initial dosage and consider possibility of a profound end/or profounded effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anestheela, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

the effects of the drug, such as drowsiness, have subsided or until the day after aneathesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital melformations associated with the use of benzodiszepines (diszepam and chlordiszepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will elso probably take longer to recover completely after VERSED for Induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anasthesis.

light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any elcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are pregnant.

your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital

VERSED® (brand of midszolem HCl/Roche) INJECTION

and innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administrated.

VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succlinytcholine or pancuronium, or against the increased intracrarial pressure noted following administration of succlinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succlinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrotate, diazepam, hydroxyzine, chubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including Ricocaine, dyclonine HCi and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertifity: Midezolam mateate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

ouses. Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible persociations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tendemes (5.6%), pain during injection (6.0%), redness (2.6%), induration (1.7%), philotitis (0.4%). Other effects (<1%) mainly following IV administration: Respiratory: Laryngospasm, bronchospasm, dyspinea, hyperventiliation, wheezing, shallow respirations, airway obstruction, techypnea. Cardiovsscular: Bigarimy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. Gastrointestinal: Acid taste, excessive salivation, retching. CNSI/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogglness, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmanes, athetoid movements, ataxia, dizziness, dysphoria, sturred speech, dysphoria, paresthesia. Special Sense: Blumertary: Hive, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at Injection site, rash, pruritus. Miscellismous: Tawning, liethargy, chilis, weakness, toothache, faint feeling, hematoma. Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DÖSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosags. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diszepern. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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Intracranial and Spinal Cord Hemodynamics in the Sitting Position in Dogs in the Presence and Absence of Increased Intracranial Pressure

Peter S. Ernst, MD, Maurice S. Albin, MD, MSc (Anes), and Leon Bunegin, BS

ERNST PS, ALBIN MS, BUNEGIN L. Intracranial and spinal cord hemodynamics in the sitting position in dogs in the presence and absence of increased intracranial pressure. Anesth Analg 1990;70:147–53.

The effect of the sitting position on cerebral blood flow (CBF), spinal cord blood flow (SCBF), and cerebral metabolic rate for oxygen (CMRO $_2$) was studied in anesthetized dogs with and without increased intracranial pressure. Blood flow measurements were made at four time periods: (a) initial supine; (b) after 5 min in the sitting position; (c) after 60 min in the sitting position; and (d) 15 min after resuming the supine position. Six dogs (group 1) served as a control group with a normal intracranial pressure (ICP). In five dogs (group 2) ICP was elevated with a parietal epidural balloon 1 h before the first measurements of blood flows were made. Saline was injected incrementally into the

balloon so as to reach a steady-state ICP of 30 mm Hg for 1 h. Elevation of ICP in group 2 resulted in significantly lower CBF, SCBF, and CMRO₂ compared with group 1. Postural changes in group 1 did not result in any significant change in blood flow measurements whereas in group 2, after 1 h in the sitting position, there were significant decreases in CBF and SCBF compared with the initial supine measurements. There was, however, no corresponding decrease in CMRO₂ in group 2 with change in position. These data suggest that both the brain and spinal cord may be at risk for ischemia during sitting position procedures under general anesthesia in the presence of elevated ICP.

Key Words: BRAIN, INTRACRANIAL PRESSURE—blood flow. ANESTHESIA, NEUROLOGIC. SPINAL CORD, PRESSURE—blood flow. POSITION, SITTING—intracranial pressure.

The sitting position has been used for many decades for neurosurgical procedures performed on the posterior fossa and high cervical region. Purported advantages of this technique include improved exposure of the surgical field, improved venous drainage, better access for the anesthesiologist to the airway and chest, and an improved view of the facial area to monitor evoked responses from cranial nerve stimulation (1). The efficacy and safety of the sitting position, however, have been a source of controversy for many years (2). Although the risk of air embolism and postural hypotension in the seated position is well documented in the literature, information regarding the effect of the seated posture on cerebral blood flow (CBF), cerebral metabolic rate of oxygen

(CMRo₂), and spinal cord blood flow (SCBF) during general anesthesia is sparse (1–4). Scheinberg and Stead (5) found that CBF decreased 21% in awake volunteers tilted 65° head-up, and Tindall et al. (6) showed an 18% decrease in internal carotid artery blood flow in anesthetized and hyperventilated patients in the sitting position, but otherwise there are few data on CBF and CMRo₂ either globally or focally, in anesthetized subjects in the seated position.

Idiopathic quadriplegia after operations with the patient in the sitting position was first described by Kurze in an address to the American Association of Neurological Surgeons in 1981 as reported by Wilder (7). Since then, other instances of quadriplegia have been observed by others, including Hitselburger and House (8), who reported quadriplegia after excision of an acoustic neuroma in the seated position. The etiology of quadriplegia after neurosurgical procedures in the seated position, however, has not been satisfactorily elucidated (7,8). One of the causative mechanisms has been thought to be ischemia of the

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cervical spinal cord secondary to decreases in spinal cord perfusion pressure. Documentation of changes in SCBF in the seated posture is, however, lacking. The possible relationship between changes in SCBF and quadriplegia after sitting position procedures was one of the driving forces behind our investigation.

The aim of this study was to examine cerebral and spinal cord hemodynamics in the sitting position in the canine by simultaneously measuring CBF, CMRo₂, and SCBF. In addition, we wanted to study the effect on CBF, CMRo₂, and SCBF in the sitting position of an increase in intracranial pressure (ICP) induced by inflation of a parietal epidural balloon.

Methods

This animal study was carried out with approval of the Institutional Laboratory Animal Care Committee of the University of Texas Health Science Center at San Antonio. Anesthesia in 11 adult mongrel dogs (14-22 kg) of either sex was induced with thiopental (25 mg/kg) administered intravenously via a 20-gauge foreleg catheter. The dogs were divided into two groups: group 1 (n = 6) had a normal ICP (<10 mm Hg), and group 2 (n = 5) had increased ICP (30 mm Hg) induced using an epidural balloon. After intubation with a cuffed endotracheal tube, a loading dose of sufentanil (2 μ g/kg IV) followed by a sufentanil infusion (0.8 μ g·kg⁻¹·h⁻¹) was given. Muscle relaxation was attained with an initial dose of pancuronium (0.1 mg/kg) and additional pancuronium (0.05 mg/kg) given as needed. Anesthesia was supplemented with isoflurane (0.5% inspired) and ventilation with air and oxygen was controlled to maintain normoxia and normocarbia. Arterial blood samples for measurement of gas tensions and pH were taken intermittently during the instrumentation and regularly during the experimental procedure. An electrocardiogram was monitored continuously.

The dogs were placed in the supine position after anesthesia induction and their heads were fixed in a stereotactic frame in a neutral position. All instrumentation was performed with the dogs in the supine position. Polyethylene catheters filled with heparinized saline were placed in each femoral artery, with one catheter being advanced to the left ventricle. A 7.0F triple-lumen pulmonary arterial catheter was also placed via the femoral approach. The legs were wrapped with elastic bandages to prevent venous pooling. Small burr holes were trephined in all dogs and a 22-gauge catheter was introduced into the sagittal sinus for venous blood sampling. The CMRo₂

was calculated as the product of hemispheric CBF and the arterial-sagittal sinus oxygen content difference. An 18-gauge needle was introduced into the cisterna magna to measure ICP continuously. The transducers for ICP and blood pressure were both referenced at the level of the external auditory meatus. In group 2, a Fogarty balloon catheter was introduced through a burr hole into the left parietal epidural space. Saline was injected incrementally into the balloon so as to reach a steady-state ICP of 30 mm Hg over a period of 1 h. After this hour of ICP stabilization, the ICP was no longer externally manipulated.

Hemodynamic measurements were monitored continuously and recorded at specific times using a Grass Instrument Co. (Quincy, Mass.) model 79 polygraph. Measurements included electrocardiogram, mean arterial pressure (MAP), right atrial pressure, pulmonary artery diastolic pressure, pulmonary capillary wedge pressure, and ICP. The triple-lumen balloon catheter was used to measure cardiac output by thermodilution and to monitor core temperature (°C). Arterial and sagittal sinus blood gas tensions were measured using an Instrumentation Laboratory, Inc. (Lexington, Mass.) pH/1306 blood gas analyzer and oxygen content was measured using an Instrumentation Laboratory, Inc. 482 co-oximeter in which the hemoglobin calibration factor was adjusted for canines.

The CBF and SCBF were measured using radioactive microspheres (9). Radioactive microspheres of mean diameter 15 \pm 5 μ m labeled with four separate γ-emitting isotopes (125I, 141Ce, 85Sr, 46Sc) were injected in a random sequence for blood flow measurements. A homogeneous mixture of 450,000-500,000 microspheres in 1.0 mL of isotonic saline was rapidly injected into the left ventricular catheter, followed immediately by a 10-mL saline flush. Ten seconds before microsphere injection, reference arterial blood samples were withdrawn at a rate of 5 mL/min for 3 min. Microsphere injections and measurements of physiologic variables were made at the following times: (a) after induction of anesthesia when the dogs were in the supine position; (b) after 5 min in the sitting position; (c) after 60 min in the sitting position; and (d) 15 min after the animal was returned to the supine position. The initial supine measurements in group 2 were made after ICP was raised to 30 mm Hg with the parietal epidural balloon; hence, the dogs in group 2 had an extra hour of anesthesia before initial supine measurements were made. The sitting position was achieved by raising the head and upper

Table 1. Blood Gas Tension, pH, and Core Temperature

		Gro	up 1		Group 2 ^a				
	Initial supine	Sitting 5 min	Sitting 60 min	Supine 15 min	Initial supine	Sitting 5 min	Sitting 60 min	Supine 15 min	
Pao ₂ (mm Hg)	174 ± 6.8	175 ± 6.7	170 ± 7.3	179 ± 6.8	184 ± 8.6	193 ± 6.7	188 ± 8.6	194 ± 13	
Paco ₂ (mm Hg)	38 ± 1.4	36 ± 1.3	39 ± 1.7	37 ± 1.3	34 ± 0.60	33 ± 0.81	37 ± 0.93	37 ± 1.4	
pН	7.35 ± 0.01	7.35 ± 0.01	733 ± 0.01	7.35 ± 0.01	7.40 ± 0.03	7.39 ± 0.02	7.36 ± 0.03	7.37 ± 0.05	
°C	37.2 ± 0.3	37.1 ± 3	37.3 ± 0.3^{b}	37.1 ± 0.4^b	36.3 ± 0.3	36.3 ± 0.3	36.0 ± 0.3	35.6 ± 0.3^{c}	

All values are mean ± sem.

Table 2. Cardiovascular Responses to the Sitting Position

		Gro	up 1		Group 2 ^s				
	Initial supine	Sitting 5 min	Sitting 60 min	Supine 15 min	Initial supine	Sitting 5 min	Sitting 60 min	Supine 15 min	
MAP (mm Hg)	135 ± 5.3	116 ± 5.0^{b}	121 ± 4.7^{b}	131 ± 4.0^{c}	134 ± 7.3	101 ± 5.6^{b}	111 ± 6.2^{b}	127 ± 3.7^{c}	
RAP (mm Hg)	2 ± 1	3 ± 2	4 ± 2	3 ± 2	0 ± 0	0 ± 0	0 ± 0	1 ± 1	
PADP (mm Hg)	5 ± 2	6 ± 2	5 ± 2	6 ± 1	3 ± 1	4 ± 0	6 ± 1	6 ± 1	
PCWP (mm Hg)	5 ± 3	5 ± 3	4 ± 3	4 ± 2	4 ± 1	5 ± 1	5 ± 2	7 ± 2	
HR (beats/min)	135 ± 15	152 ± 11^{b}	140 ± 12	123 ± 11^{c}	129 ± 12	152 ± 8.6^{b}	152 ± 18	$124 \pm 10^{\circ}$	
$CI (L \cdot min^{-1} \cdot m^{-2})$	2.87 ± 0.31	2.43 ± 0.31^{b}	2.24 ± 0.13^{b}	2.79 ± 0.35^{c}	2.46 ± 0.22	2.05 ± 19^{b}	1.83 ± 0.23^b	$2.32 \pm 0.21^{\circ}$	
SVRI (dyne·s·cm ⁻⁵ ·m ⁻²)	3893 ± 385	3967 ± 431^b	4250 ± 269^b	3955 ± 488^{c}	4483 ± 464	4055 ± 332^{b}	5207 ± 757^b	4490 ± 419°	
SVI (ml·beats ⁻¹ ·m ⁻²)	23 ± 4.3	16 ± 1.8^{b}	17 ± 1.7^{b}	$24 \pm 3.8^{\circ}$	20 ± 1.4	14 ± 1.8^b	13 ± 2.2^b	$19 \pm 2.0^{\circ}$	

CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; PADP, pulmonary artery diastolic pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index. All values are mean \pm sem.

were raised to heart level by flexing at the groin.

body to a 60° angle from the horizontal; the front legs

were secured at the sides of the dog and the rear legs

Postural changes were performed over a period of 2 min. During all postural changes, MAP and ICP were referenced at the level of the external auditory meatus; right atrial pressure, pulmonary artery diastolic pressure, and pulmonary capillary wedge pressure were consistently referenced at heart level. After the last set of measurements, the animals were killed with IV KCl injection, and the brain and spinal cord were removed, formalin-fixed, and sectioned. Radioactivity of the tissue and blood samples was measured by counting for 1 min on a multichannel Auto Gamma scintillation spectrometer (Packard Instrument Co., Inc., Downers Grove, Ill.). Blood flows were derived by computer calculation as previously described (10), using the following formula: F = $(CT/CB) \times 100$, where F =tissue blood flow (mL·100 g^{-1} ·min⁻¹); CT = counts per gram of tissue; <math>CB =counts per milliliter per minute of reference arterial blood.

The data were compared using a two-way analysis of variance followed by Student's Neuman-Keuls test, with repeated measures design, followed by specific post-tests where indicated. Statistical significance was taken to be P < 0.05 and all values in text and tables are shown as mean \pm sem.

Results

Table 1 shows blood gas tensions, pH, and temperature data in both groups. Table 2 shows hemodynamic variables in both groups. Table 3 shows CBF, SCBF, cerebral perfusion pressure (CPP), ICP, CMRo₂, and cerebral vascular resistance (CVR = CPP/CBF) data in both groups. Arterial blood gases remained within normal physiological limits in both groups. There was a small but statistically significant difference in temperature between groups (37.2° ± 0.3° C in group 1, $36.1^{\circ} \pm 0.3^{\circ}$ C in group 2). There was no significant difference in the two groups in heart rate (HR), MAP, right atrial pressure, pulmonary

Initial supine measurements made 1 h after increase in intracranial pressure.

 $^{^{}b}P < 0.05$ vs corresponding group 2 value.

 $^{^{}c}P < 0.05$ vs corresponding supine value; P < 0.05 vs initial sitting value.

Initial supine measurements made 1 h after increase in intracranial pressure.

 $^{^{}b}P < 0.05$ vs initial supine value. ^cP < 0.05 vs initial sitting value.

Table 3. Brain and Spinal Cord Hemodynamics

		Grou	ıp 1		Group 2 ^a				
Region	Initial supine	Sitting 5 min	Sitting 60 min	Supine 15 min	Initial supine	Sitting 5 min	Sitting 60 min	Supine 15 min	
Hemispheric (mL·100 g ⁻¹ ·min ⁻¹)	36.9 ± 3.3^b	43.8 ± 8.1^{b}	33.4 ± 3.2^b	36.3 ± 3.0^b	24.1 ± 3.1	22.1 ± 3.0	$15.8 \pm 4.2^{c,d}$	15.7 ± 4.8	
Cerebellum (mL·100 g ⁻¹ ·min ⁻¹)	41.9 ± 4.8^{b}	44.8 ± 9.7	35.0 ± 4.2^{b}	40.4 ± 4.7^{b}	27.7 ± 3.3	24.9 ± 6.0	$19.1 \pm 4.0^{\circ}$	19.3 ± 5.1	
Brainstem (mL·100 g ⁻¹ ·min ⁻¹)	40.8 ± 4.7	42.9 ± 9.2	33.5 ± 3.2^b	39.2 ± 4.6^{b}	27.8 ± 3.0	32.1 ± 4.5	$18.9 \pm 4.1^{c,d}$	19.5 ± 5.2^d	
Cervical (mL·100 g ⁻¹ ·min ⁻¹)	37.5 ± 3.8^{b}	37.7 ± 11.0	33.7 ± 3.2^b	36.7 ± 3.4^b	25.8 ± 3.5	27.9 ± 5.5	$18.3 \pm 4.4^{c,d}$	17.8 ± 5.1^d	
Thoracic (mL·100 g ⁻¹ ·min ⁻¹)	37.4 ± 3.7^{b}	38.4 ± 9.0	35.4 ± 2.8^b	35.7 ± 3.1^b	25.4 ± 3.7	27.8 ± 4.8	$17.5 \pm 4.2^{c,d}$	17.9 ± 5.1^d	
Lumbar (mL·100 g ⁻¹ ·min ⁻¹)	37.3 ± 3.6	34.7 ± 10.4	32.7 ± 4.0	37.0 ± 3.0^{b}	25.3 ± 4.2	23.0 ± 7.3	20.2 ± 5.1	18.2 ± 5.3	
CPP (mm Hg)	130 ± 5.2^{b}	$116 \pm 5.0^{b,c}$	121 ± 4.7	126 ± 4.3^{b}	104 ± 7.3	87 ± 7.6	99 ± 4.8	95 ± 5.9	
ICP (mm Hg)	5 ± 1^{b}	$-2 \pm 2^{b,c}$	$-2 \pm 2^{b,c}$	$5 \pm 1^{b,d}$	30 ± 0	14 ± 3^{c}	12 ± 3^{c}	32 ± 4^d	
CMRo ₂ (mL O ₂ ·100 g ⁻¹ ·min ⁻¹)	2.46 ± 0.15^b	2.75 ± 0.47	2.42 ± 0.22	2.97 ± 0.36	1.56 ± 0.34	1.98 ± 0.3	1.57 ± 0.50	1.85 ± 0.53	
CVR (mm Hg·mL ⁻¹ ·100 g·min)	3.59 ± 0.28	2.98 ± 0.47	3.61 ± 0.34	3.49 ± 0.34	4.59 ± 0.67	4.39 ± 0.91	15.4 ± 10	23.9 ± 18	

CMRo2, cerebral metabolic rate for oxygen; CPP, cerebral perfusion pressure; CVR, cerebral vascular resistance; ICP, intracranial pressure. All values mean \pm sem.

artery diastolic pressure, pulmonary capillary wedge pressure, cardiac index, systemic vascular resistance index, or stroke volume index. However, CPP (CPP = MAP - ICP) and ICP were significantly different between groups during both supine and sitting measurements. The CPP did not decrease below 72 mm Hg in either group.

There were significant differences associated with changes in posture and with passage of time in both groups involving HR, cardiac index, systemic vascular resistance index, stroke volume index, and ICP. The CPP initially decreased significantly in group 1 in the seated position, but returned back to baseline levels after 1 h in the seated position. In group 2, CPP did not change significantly during the experiment.

Average CBF in each anatomic area was determined by pooling data from individual brain sections. Hemispheric, cerebellar, and brainstem blood flows decreased significantly in group 2 but hemispheric, cerebellar, and brainstem blood flows did not change significantly with changes in posture or across time in group 1. In group 2, hemispheric, cerebellar, and brainstem blood flows were significantly depressed after 60 min in the sitting position and remained below baseline levels 15 min after the supine position was resumed. There was a significant difference between groups in CMRo₂, but CMRo₂ did not vary significantly with changes in posture or across time within each group. Although extracerebral venous drainage can hinder an accurate determination of CMRo₂, our technique sampled the posterior portion of the sagittal sinus. This technique permits only a small and constant contamination in the dog by extracerebral blood through the anterior ethmoidal veins (11). Although CVR increased in group 2 during the experimental protocol, this increase was not statistically significant.

The SCBF was measured by averaging data from sections of the cervical, thoracic, and lumbar regions. There were significant differences between group 1 and 2 in all cord regions. In group 1, there were no significant changes in SCBF in any region of the cord related to changes in posture or across time. However, in group 2, there were significant decreases in cervical and thoracic blood flows after 1 h in the sitting position, flows that remained depressed 15 min after the supine position was resumed.

Discussion

Although the sitting position is used to provide better surgical exposure during posterior fossa and neurosurgical procedures on the cervical spine and cord, the effects of this posture on cerebrovascular and spinal cord dynamics have never been delineated in

Initial supine measurements made 1 h after increase in intracranial pressure.

 $^{^{}b}P < 0.05$ vs corresponding group 2 value.

 $^{^{}c}P < 0.05$ vs corresponding supine value. $^{d}P < 0.05$ vs initial sitting value.

either the awake or anesthetized subject. The paucity of literature in this area may be due to the unproven assumption that CBF and SCBF are not altered by postural changes as long as CPP is maintained within autoregulatory limits (50–150 mm Hg) (5,6). Using the nitrous oxide technique of Kety and Schmidt for measurement of CBF, Scheinberg and Stead (5) showed a statistically significant (P < 0.05) 21% drop in CBF when awake subjects were tilted head-up 65° from the horizontal. Subjects in their study did not have their legs wrapped nor were their legs raised to heart level. In our study, we attempted to mimic the clinical situation by raising the animals' legs to heart level and by wrapping the legs with elastic bandages. The head and upper body were raised to 60° from the horizontal.

Because we attempted to mimic the clinical setting, the anesthetic was chosen from a survey of institutions administering a large number of anesthetics in the sitting position. A narcotic-based anesthetic was selected based on this survey. We also found that isoflurane was commonly used as a supplement in the clinical situation. After a few trials in our laboratory, isoflurane at a constant inspired concentration of 0.5% proved to provide an adequate surgical plane of anesthesia in our dogs; during instrumentation (including burr hole placement), no changes in HR or MAP could be discerned (12).

The cardiovascular responses to the sitting position in our study with dogs were similar to those found in previous studies of anesthetized humans (1,2,13). There were significant reductions in MAP, cardiac index, and stroke volume index in both our groups of dogs on assumption of the sitting position that persisted until the supine position was resumed. The HR and systemic vascular resistance index increased significantly in both groups in the seated position and remained elevated until the supine position was resumed.

The differences between our normal (1) and increased ICP groups (2) were marked in terms of CBF and SCBF. It should be noted that there were no significant differences between groups at any time period in $Paco_2$, pH, or Pao_2 . Baseline hemispheric, cerebellar, cervical, and thoracic blood flows were significantly less in the increased ICP group (2) than in the normal ICP group (1). There was also a trend for brainstem and lumbar blood flows to decrease, though not significantly, in group 2. Baseline levels of CPP in group 2 in the supine position averaged 104 ± 7.3 mm Hg. In the normal brain, this perfusion pressure should be adequate to maintain CBF. However, in the presence of a mass lesion, as in group 2, autoregulation of CBF may be altered (14). Therefore,

in group 2, either the autoregulatory curve for CBF is shifted to the right or arterial vessels in the cerebral circulation are collapsing because of intracranial hypertension. As ICP increases, cerebrovascular dilation takes place. The arteriolar diameter increases and the arterial vascular system becomes more readily compressible owing to vascular wall thinning (15). Thus, when vasodilation is maximal, any small decrease in CPP or an increase in ICP may cause a marked decrease in CBF. If no obstruction in the subarachnoid space is present, an elevated ICP should be transmitted throughout the space and similarly affect both brain and spinal cord. As a recent study (16) shows that autoregulation of blood flow is similar in the cerebral and spinal cord circulations, it is not unexpected that both cervical and thoracic blood flow were also initially reduced in our dogs when placed in the sitting position.

Across time and with changes in posture, the dogs in the normal ICP group (1) had no change in either CBF or SCBF from baseline levels. Starting from a lower baseline level, CBF and SCBF in dogs in the increased ICP group did not decrease within the first 5 min of assuming the sitting position. However, after 1 h, there were significant decreases in hemispheric, cerebellar, brainstem, cervical, and thoracic blood flows in group 2. Flows decreased despite maintenance of CPP and a significant decrease in ICP (Figure 1). The decrease in CBF was paralleled by an increase in CVR. The increase in CVR could be indicative of a general decrease in caliber of cerebral vessels or due to a collapse of a portion of the vessels. A possible explanation for the decrease in CBF over time and with the change in posture would be formation of edema from maturation of the lesion produced by the epidural balloon. However, ICP did not increase in the seated posture period and cerebral edema would not explain the significant decrease in SCBF.

In critically ill patients with elevated ICP, Ropper et al. (17) showed that when the head was raised 60° ICP often decreased. However, the decrease in ICP was sometimes associated with a reduced intracranial compliance. Although the mechanism for the simultaneous decrease in compliance and ICP has not been defined, it could explain our findings of reduced CBF and SCBF in the face of decreased ICP and preserved CPP occurring with the change to the seated position.

The implications of a marked decrease in CBF due to raising the head to 60° are important. Although it is well documented that the seated position invites the risk of air embolism and systemic hypotension, our data indicate that when a mass lesion is present, a real danger of cerebral hypoperfusion exists. As

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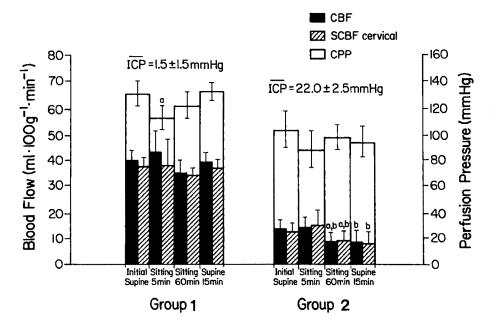


Figure 1. Effect of the sitting position on cerebral and cervical spinal cord blood flow. (■) CBF, cerebral blood flow in mL·100 g⁻¹·min⁻¹; (☒) SCBF cervical, cervical spinal cord blood flow in mL·100 g⁻¹·min⁻¹; (□) CPP, cerebral perfusion pressure in mm Hg; ICP, mean intracranial pressure in mm Hg. "Significant difference from initial supine value. "Significant difference from initial sitting value.

CMRo₂ did not decrease in parallel with CBF in the seated position, the risk for ischemia becomes more evident. This uncoupling of CBF and CMRo₂ is a potential hazard in the patient with a mass lesion. The consequences of a decrease in global CBF are potentially even more serious if a state of "vasomotor paralysis" develops in the region of a mass lesion as described by Langfitt (18); tissue surrounding a mass lesion often becomes ischemic resulting in hypoxia, hypercarbia, and acidosis, and the blood vessels, losing their ability to autoregulate, become maximally dilated (19). These ischemic zones may be especially vulnerable to reductions in CBF generated by the sitting position.

The decrease in SCBF, especially cervical blood flow, suggests the possibility of spinal cord hypoperfusion. Kurze reported a series of case reports from the literature of idiopathic quadriplegia after a surgery in the sitting position (7). The lower cervical spinal cord, because it is farthest from collateral pathways, appears to be most vulnerable to ischemia (20); blood to the spinal cord flows from the extreme ends of the spinal cord via the cervical cord vessels and the paired anterior and posterior spinal arteries (21). Anatomic correlations of these physiologic data about cervical cord susceptibility to ischemia are available. Turnbull et al. (22) reported the presence of only one anterior radicular artery supplying the cervical cord in autopsy material. Szilagyi et al. (23) also reported the presence of but one radicular feeding artery in the cervical cord. In a postmortem review, Manners (24) reported that 45 of 215 spinal cords had just one anterior radicular artery in the cervical cord. Data confirming these anatomic considerations are available in Jellinger's (25) study of ischemic cord lesions in 60 cases of advanced atherosclerosis. He noted ischemia preferentially located between C-5 and T-2. Fried et al. (26) found in rhesus monkeys that the most vulnerable region to ischemia is at C-6, because the blood flow splits into compartments flowing up and down the anterior spinal artery. Hence, the lower cervical cord would be farthest from collateral pathways via the vertebral and intercostal arteries (21). Apparently, the cervical cord has a marginal blood flow for an area of high function. The anterior spinal artery is critical in the formation of the cervical radicular artery and its most cephalad intermediate feeder arteries are spinal branches of the vertebral arteries (23). Decreases in vertebral artery flow would also tend to decrease flow into the substance of the cervical cord.

Wilder (7) hypothesized that acute flexion of the cervical spine with the patient in the sitting position under general anesthesia may produce sufficient stretch of the spinal cord to alter autoregulation by mechanically affecting the spinal cord vasculature. This proposal was based on work done by Brieg (27) that showed the cervical spinal cord increases in length when the neck moves from full extension to full flexion; the location of the maximal change in length is approximately C-5. The dogs in our group 1 did not show any changes in SCBF with the change in posture. However, in group 2 perhaps the added compression caused by increased cerebral spinal fluid pressure caused mechanical narrowing of blood vessels supplying the cervical and thoracic spinal cord. The resultant decrease in spinal cord blood flow might be detrimental to individuals with atherosclerosis and those with only one anterior radicular artery supplying the cervical cord, as cited above.

The seated position is still the subject of controversy among both neurosurgeons and anesthesiologists. Before our study, the effect of the seated posture on CBF, CMRo₂, and SCBF had not been studied in anesthetized subjects. In a mammalian model, our data indicate that CBF and SCBF are compromised by the seated posture when a mass lesion is present. Notably, the decrease in CBF initiated by the change in position is unaccompanied by a reduction in CMRo₂. Our results also raise the question as to what comprises an adequate CPP in the seated position and how autoregulation is affected. If the sitting position places the brain and spinal cord at risk for ischemia in those with mass lesions, perhaps alternative positions should be sought in these patients.

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Antibody Assays for the Detection of Patients Sensitized to Halothane

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Sera from patients with a clinical diagnosis of halothane hepatitis have been shown to contain antibodies that react with liver microsomal proteins (100, 76, 59, 57, and 54 kDa) covalently altered by the trifluoroacetyl (TFA) halide metabolite of halothane. In the present study, rapid and sensitive enzyme-linked immunosorbent assays for the detection of these antibodies have been evaluated. A recently described method that utilizes TFA-rabbit serum albumin as test antigen was studied employing a large population of halothane hepatitis and control patients. Several problems were discovered with the assay that were not previously recognized. The assay was then compared directly with

methods that utilize as test antigens either liver microsomes or purified TFA proteins from halothane-treated rats. Sixty-seven percent of patients with a clinical diagnosis of halothane hepatitis tested positive for antiòodies when the test antigens were either TFA-rabbit serum albumin or liver microsomes. This value was increased to 79% when the purified TFA-57 kDa, TFA-76 kDa, and TFA-100 kDa proteins were used as test antigens. These results indicate that the specificity and sensitivity of enzyme-linked immunosorbent assay methods for the detection of patients' antibodies may be increased significantly by utilizing the purified TFA microsomal proteins as test antigens.

Key Words: ANESTHETICS, VOLATILE—halothane. LIVER, HEPATITIS. IMMUNE RESPONSES—in halothane hepatitis.

The inhalation anesthetic halothane (CF₃CHClBr) produces two types of hepatotoxicity (1,2). The first, a mild self-limited postoperative hepatotoxicity, is characterized by transient elevations in plasma levels of liver transaminase enzymes and appears in 20%–25% of patients anesthetized with halothane. The rarer and much more severe complication (halothane hepatitis) occurs in one in 10,000–30,000 patients exposed to halothane and may lead to massive hepatic necrosis and death.

Considerable clinical and experimental evidence suggests that halothane hepatitis is an immune mediated toxicity (2–6). The often observed clinical features of halothane hepatitis include arthralgias, eosinophilia, fever, rash, and prior exposure to the

anesthetic. These characteristics are all commonly associated with drug hypersensitivity reactions. Most important, the sera of many patients with a clinical diagnosis of halothane hepatitis have been found to contain specific antibodies that react with halothaneinduced liver antigens (neoantigens), whereas the sera of patients with other forms of hepatitis do not contain antibodies of this specificity. It has recently been shown that the neoantigens are formed by the covalent interaction of the reactive oxidative trifluoroacetyl halide metabolite (CF3COX, TFA-X) of halothane (7,8), with at least five distinct classes of liver microsomal proteins (100, 76, 59, 57, and 54 kDa) (7–10). These findings suggest that the TFA neoantigens represent the immunogens that have elicited the observed antibody responses and may therefore play an immunopathological role in the development of the liver injury associated with halothane hepatitis.

An assay for the detection of the antibodies directed against the TFA neoantigens has potential clinical importance for several reasons. First, the presence of the antibodies in the sera of patients previously exposed to halothane would indicate prior sensitization and would thus identify these patients as being at increased risk for developing a hypersen-

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sitivity reaction upon further exposure to halothane. Second, these same antibodies have been shown to react with liver microsomal neoantigens produced by the structurally related oxidative acyl halide metabolite of enflurane (CHF₂OCF₂COX), suggesting the potential for a cross-sensitization reaction after enflurane exposure (11,12). Third, the assay can be used to monitor sensitization to halothane in animal model studies of the immunopathological mechanism of halothane hepatitis (13–16).

Two general types of immunochemical assays have been reported for the detection of the patients' antibodies. The first method is immunoblotting. In this procedure, test antigens are microsomal proteins derived from halothane-treated rabbits or rats. The proteins are first separated into constituent components by sodium dodecylsulfate-polyacrylamide gel electrophoresis and then transferred electrophoretically to the surface of nitrocellulose paper. Using this method, 42 of 68 (62%) patients with a clinical diagnosis of halothane hepatitis have been found to test positive for the halothane-induced antibodies (7). Although this approach provides important information concerning the apparent molecular masses of the neoantigens reacting with the patients' antibodies, it is laborious and time consuming. It also has the potential of being inherently less sensitive than other methods because it involves the protein-denaturing conditions of sodium dodecyl sulfate-polyacrylamide gel electrophoresis. This could lead to a decreased level of response if the patients' antibodies were directed against, at least in part, conformational epitopes of the TFA neoantigens (17).

The second immunochemical assay that has been used for the detection of antibodies in the sera of patients with a clinical diagnosis of halothane hepatitis is based on the more rapid, facile, and potentially more sensitive enzyme-linked immunosorbent assay (ELISA) methodology in which test antigen is applied directly to the wells of a microtiter plate. One reported ELISA procedure utilizes microsomes from halothane-treated rabbits as test antigen. Using this approach, investigators have demonstrated the presence of the antibodies in the sera of 16 of 24 (67%) (18) and 28 of 39 (72%) (19) of the patients with a clinical diagnosis of halothane hepatitis. In another ELISA assay, one that uses the TFA hapten as test antigen in the form of TFA-rabbit serum albumin (TFA-RSA), positive responses from patients with a clinical diagnosis of halothane hepatitis ranged from two of six (33%) patients (3) to five of six patients (83%) (20).

In the present study, the ELISA procedure that uses TFA-RSA as test antigen has been more completely evaluated using a larger population of sera

from patients with a clinical diagnosis of halothane hepatitis and control patients than previously reported. It was found that this assay is not as reliable as previously indicated by the most recent report using this procedure (20). The assay has also been compared directly to ELISA techniques that use as test antigen either total liver microsomal protein from halothane-treated rats or specific TFA neoantigens that have been purified recently from the livers of halothane-treated rats. The results suggest that the future use of all of the purified TFA antigens might improve the ELISA method such that nearly all sensitized patients may be identified.

Materials and Methods

Chemicals

Casein (Hammarsten grade) was purchased from Gallard-Schlesinger (Carl Place, N.Y.). Horseradish peroxidase-conjugated goat-antihuman immunoglobulin G and goat-antirabbit immunoglobulin G were from Tago Immunodiagnostic Reagents (Burlingame, Calif.). Halothane was from Halocarbon Laboratories Inc. (Hackensack, N.J.) and was purified by distillation before use. Trifluoroacetyl-rabbit serum albumin (21), hapten-specific anti-TFA sera (21), and liver microsomes from halothane-treated rats were prepared as described previously (22). The TFA-100 kDa, TFA-76 kDa, and TFA-57 kDa proteins were purified from microsomes of halothane-treated rats by diethylaminoethyl (DEAE) Sepharose anion-exchange chromatography, followed by hydroxylapatite highpressure liquid chromatography (23,24). A detailed description of the purification and characterization of these proteins will be the subject of future papers.

Human Antisera

Sera were obtained from patients with a clinical diagnosis of halothane hepatitis as described in detail elsewhere (18,19). Briefly, the sera of patients with unexplained hepatitis after halothane anesthesia were negative for serologic markers of hepatitis A and B infection, cytomegalovirus, and Epstein–Barr virus, and none had received any potentially hepatotoxic drugs or had a history of alcohol excess. In patients with a clinical diagnosis of halothane hepatitis, the interval between halothane exposure and the onset of hepatic injury ranged from 3 to 28 days (median, 8 days). The interval between exposure and sera collection was 4–67 days (median, 20 days), and time to death (31%) was 6–74 days (median, 28 days).

Sera were also collected from the following control patients who had had no halothane hepatitis at Kings College Hospital, London, U.K. and at the Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland. These control patients included those with multiple halothane exposures without developing evidence of liver dysfunction, normal control subjects (i.e., without prior halothane, hepatitis, or liver dysfunction), subjects exposed to subclinical doses of halothane (anesthesiologists, operating room and recovery room nurses), patients with primary biliary cirrhosis, patients with acute fulminant liver disease, patients with chronic active liver disease, and patients with viral hepatitis who had been exposed to halothane.

ELISA Procedures

All assays were performed in triplicate in the wells of polystyrene microtiter plates (Dynatech Laboratories, Chantilly, Va.) in a total reaction volume of 100 μ L, and plate washings were conducted with a Titertek automated plate washer (Flow Laboratories, McLean, Va.).

TFA-RSA as antigen. Microtiter plates were coated overnight for 16 h at 4°C with TFA-RSA or RSA, diluted to 10 μ g/mL in phosphate-buffered saline (PBS, pH 7.4) or PBS alone. They were washed eight times with 10 mmol/L Tris-saline pH 7.6, containing 0.5% (wt/vol) casein and 0.01% (wt/vol) Thimerosol (0.5% casein buffer) to remove unbound material and to block unoccupied protein-binding sites. Patients' sera, diluted 1:100 in PBS, were added to the wells, and plates were incubated for 2 h at room temperature. The plates were then washed four times with 0.5% casein buffer, followed by the addition of horseradish peroxidase-conjugated goat-antihuman immunoglobulin G, diluted 1:500 in 0.5% casein buffer. After incubation for 3 h at room temperature, the plates were washed four times with 0.5% casein buffer, followed by four washes with PBS. Horseradish peroxidase substrate mixture, consisting of ophenylenediamine (0.4 mg/mL) and H_2O_2 (30%, 0.8) μ L/mL, added immediately before use) in 50 mmol/L sodium phosphate containing 25 mmol/L citric acid (pH 5.0), was added to the wells and after 2 min the reactions were stopped by the addition of 4 N H_2SO_4 (50 μ L). The optical density (OD) of the solutions in each of the wells was immediately determined at 492 nm utilizing a Titertek automatic plate reader (Flow Laboratories). The OD results from the TFA-RSA and

RSA wells were corrected for nonspecific reactions by subtracting from them the values obtained from the wells that contained PBS in place of TFA-RSA or RSA. The TFA-RSA results were further corrected for reactions directed against carrier protein RSA by subtracting from them the results of the RSA wells.

Liver microsomes and purified trifluoroacetyl proteins as antigens. Microtiter plates were coated overnight for 16 h at 4°C with control microsomes, microsomes from halothane-treated rats, or purified TFA proteins (100, 76, or 57 kDa) diluted to 10 μ g/mL in PBS. Before the addition of the patients' sera, reactivity against normal liver constituents was reduced by mixing the sera with control rat liver microsomes (1 mg/mL) overnight for 16 h at 4°C. This was followed by centrifugation at 100,000 g for 12 min at 4°C in a TL-100 ultracentrifuge (Beckman Instruments, Fullerton, Calif.) to separate the microsomes from absorbed sera. The remainder of the assay was as described for the assay utilizing TFA-RSA as test antigen. The OD results were corrected by subtracting from them the values obtained from the blank PBS wells. The results obtained with the halothane microsomes were further corrected by subtracting from them the results from the control microsomes (18).

Gel Electrophoresis and Immunoblotting

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immunoblotting of liver microsomes from halothane-treated rats and purified rat liver TFA-57 kDa, TFA-76 kDa, and TFA-100 kDa proteins with patients' sera or hapten-specific anti-TFA sera were performed as described in detail elsewhere (7,11,12).

Results

Sera from 44 patients, previously diagnosed clinically as having halothane hepatitis, were tested for the presence of halothane-induced antibodies by the TFA-RSA ELISA procedure (Figure 1). Twenty-six (59%) of the patients tested positive for the antibodies by this procedure. Surprisingly, 15 of 126 (12%) of all patients without a clinical diagnosis of halothane hepatitis also tested positive for the antibodies. The sera of these patients, in contrast to the sera of the halothane hepatitis patients, did not react with the TFA neoantigens on transfer blots of liver microsomes from halothane-treated rats (results not shown). Many of the sera from halothane hepatitis patients, 12 of 44

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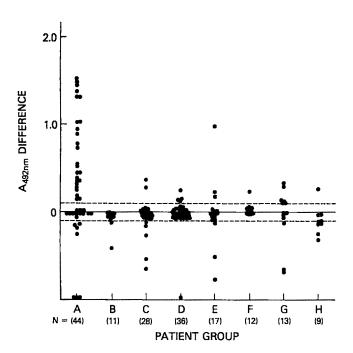


Figure 1. Screening of various sera for antibodies that react with the TFA hapten of TFA-RSA. A, halothane hepatitis patients; B, patients that have received multiple halothane exposures without developing liver damage; C, normal control patients; D, individuals who have received subclinical exposure to halothane, such as anesthesiologists and operating-room and recovery-room nurses; E, patients with primary biliary cirrhosis; F, patients with acute fulminant hepatic failure; G, patients with chronic active liver disease; and H, patients with viral hepatitis who have been exposed to halothane. The assays were conducted as described in Materials and Methods. A_{492} difference = $(A_{492}$ TFA-RSA) – $(A_{492}$ RSA), and N = the number of individuals in each group. A positive or negative reaction is defined as a value that is three standard deviations outside of the range of results obtained from the sera of 22 normal control patients (indicated by broken lines).

(27%) and 37 of 126 (29%) of all other patients' sera, also reacted with the carrier protein RSA, as illustrated by the negative OD values obtained from these samples (Figure 1).

The sensitivity of the TFA-RSA ELISA procedure was compared directly with ELISA methods that utilized as test antigens either liver microsomes from halothane-treated rats or the rat liver TFA neoantigens of 57, 76, and 100 kDa that had been isolated from liver microsomes of halothane-treated rats (23,24). Electrophoretic and transfer blot analyses of the isolated neoantigens indicated that they were relatively pure (Figure 2A) and contained the covalently bound TFA hapten as determined by their reaction with the hapten-specific anti-TFA antibodies (Figure 2B). It was found that of the 24 halothane hepatitis patients tested, 67% tested positive for antibodies when the test antigens were either TFA-RSA or liver microsomes from halothane-treated rats (Table 1). This value was increased to 79% of patients

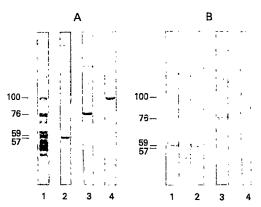


Figure 2. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immunoblotting of liver microsomes from halothanetreated rats and purified rat liver TFA-57 kDa, TFA-76 kDa, and TFA-100 kDa neoantigens. 1, liver microsomes from halothanetreated rats; 2, TFA-57 kDa; 3, TFA-76 kDa; and 4, TFA-100 kDa. A, sodium dodecyl sulfate-polyacrylamide gel electrophoresis gels that were stained for protein with Coomassie Blue dye. B, immunoblots of the gels that were stained immunochemically with hapten-specific anti-TFA antibodies.

when the TFA-57 kDa, TFA-76 kDa, and TFA-100 kDa proteins were used as test antigens. This apparent increase in assay sensitivity was observed even though 63% of patients reacted with each of the purified TFA neoantigens, as not all patients' sera reacted with each of the three antigens. Three of the patients, patients 3, 6, and 7, tested negative by each of the procedures.

Discussion

In this study, an examination of halothane hepatitis and control patients by the TFA-RSA ELISA procedure, in a population larger than those previously reported (3,20), has led to the conclusion that this ELISA assay has limited application for detecting individuals sensitized to halothane. The previously reported method (20) is neither specific nor sensitive enough to be reliable for the detection of circulating antibodies in halothane hepatitis patients. For example, in the present study we found that 12% of all patients without a clinical diagnosis of halothane hepatitis tested positive for sensitization by this assay. The reason for this finding is unclear at the present time. Moreover, only 59% of the 44 halothane hepatitis patients tested positive for the presence of halothane-induced antibodies (Figure 1). One contributing factor for the lack of response of several of the halothane hepatitis patients might be due to the reactivity of their sera with carrier protein RSA. This could effectively lead to apparent negative test results in patients who might have low levels of anti-TFA reacting antibodies. A possible reason for the reaction

<u>Table 1</u>. Screening of Sera From 24 Halothane Hepatitis Patients for Antibodies by Enzyme-Linked Immunosorbent Assay Methods Utilizing Different Test Antigens

		A	ntigen		
Patient	TFA-RSA	Microsomes	57 kDa	76 kDa	100 kDa
1	<u>-</u>	+	+	+	+
2	-	+	+	+	+
3	_	-	_	_	
4	_	_	+	+	+
5	_	+	+	+	****
6	-	-		_	
7	-	_	****	-	***
8	_	+		+	+
9	+	+	+	+	+
10	+	+ .	+	_	
11	+	_	+	+	****
12	+	+		_	+
13	+	+	+	+	+
14	+	_	+	+	+
15	+	+	+	+	+
16	+	+		_	••••
17	+	_		_	****
18	+	+	-	_	+
19	+	-	+	+	+
20	+	+	+	+	*****
21	+	+	+	+	+
22	+	+	+	-	+
23	+	+	+	+	+
24	+	+		+	+
	16/24 (67%)	16/24 (67%)	15/24 (63%)	15/24 (63%)	15/2 4 (53%)
			ſ	19/24 (79%)	1

The assays were conducted as described in Materials and Methods using the same 24 sera samples for each of the types of test antigens. A positive reaction is defined as an optical density reading at 492 nm that is three standard deviations above the range of values obtained from the sera of eight control patients.

of the patients' sera with RSA might be due to the presence of antialbumin autoantibodies that cross-react with RSA (25). If this were the case, the specificity and sensitivity of the assay might be increased by absorbing the patients' sera with human serum albumin before performing the assay.

The low sensitivity of the TFA-RSA ELISA procedure might also be attributed to the fact that the antibodies in the sera of most of the halothane hepatitis patients are directed against epitopes consisting of both the TFA hapten and specific structural features of the individual TFA-altered proteins and not of the TFA hapten alone (7,8). This suggests that some of the patients' antibodies would bind only weakly to TFA-RSA and might therefore be displaced during the washing steps of the ELISA assay procedure.

By contrast, the ELISA procedure based on the use of liver microsomes from halothane-treated animals

as test antigen should be more specific and sensitive than the TFA-RSA assay, as the antigens used are the liver microsomal TFA neoantigens. Indeed, no false-positive tests have been reported using this assay (18). Nevertheless, approximately 30% of the patients with a clinical diagnosis of halothane hepatitis in the present study lacked the halothane-induced antibodies as tested by this method (Table 1) (18,19), suggesting that these patients either did not produce an antibody response against the TFA neoantigens or that their antibody titers were below the detection limits of the assay.

The sensitivity of the ELISA procedure should be increased significantly by using the purified TFA neoantigens as test antigens, as this would permit a higher concentration of the epitopes of each antigen to come in contact with the patients' antibodies than would be expected to occur when a mixture of microsomal proteins is used as test antigen. Results utilizing purified rat liver microsomal TFA-57 kDa, TFA-76 kDa, and TFA-100 kDa neoantigens indicate that this is the case. Indeed, four of the halothane hepatitis patients who tested negative by the microsomal ELISA method were found to contain halothane-induced antibodies by this method (Table 1, patients 4, 11, 14, and 19).

It is anticipated that the sensitivity of the ELISA assay will be improved significantly once all of the TFA neoantigens are included as test antigens, as some patients may not be sensitized to the TFA-57 kDa, TFA-76 kDa, or TFA-100 kDa neoantigens. This idea will be examined in the future on an even larger population of halothane hepatitis and control patients when all of the TFA neoantigens become available. Eventually, the TFA neoantigens will be purified from human liver. These neoantigens should prove to be the best test antigens for the detection of sensitized patients.

Reports have appeared of hepatotoxicity associated with enflurane (26,27) and of hepatic dysfunction (28) and hepatic failure after isoflurane anesthesia (29). These anecdotal findings all suffer from the lack of a definitive clinical confirmatory test. Reports have, however, shown that enflurane and isoflurane can also produce acylated liver microsomal adducts, similar to those produced by halothane, although at lower levels (11,12). It has also been found that antibodies in halothane hepatitis patients can react with the enflurane-induced neoantigens. These findings suggest that a strategy similar to that used with the halothane-induced neoantigens could be used to develop a rapid, reproducible, and clinically important assay for detection of patients who may be sensitized to enflurane and isoflurane.

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Pediatric Anesthesia Morbidity and Mortality in the Perioperative Period

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COHEN MM, CAMERON CB, DUNCAN PG. Pediatric anesthesia morbidity and mortality in the perioperative period. Anesth Analg 1990;70:160–7.

One of the most frequent questions asked of a pediatric anesthesiologist is "What are the risks of anesthesia for my child?" Unfortunately, few studies have examined the consequences of general anesthesia in children. We used data from a large pediatric anesthesia follow-up program at Winnipeg Children's Hospital (1982–1987) to determine rates of perioperative adverse events among children of different ages. A check-off form was completed by a pediatric anesthesiologist for each case (n=29,220) and a designated follow-up reviewer examined all anesthesia forms and hospital charts to ascertain adverse effects for children less than 1 mo, 1-12 mo, 1-5 yr, 6-10 yr, and 11-16 yr of age in the intraoverative, recovery room, and postoperative periods. The majority of the children were healthy, and 70% had no

preoperative medical conditions. Infants less than 1 mo old were more likely to be undergoing major cardiac or vascular procedures, whereas the older children had mainly orthopedic or otolaryngologic procedures. Infants less than 1 mo old had the highest rate of adverse events both intraoperatively and in the recovery room. The main problem in this age group was related to the respiratory and cardiovascular systems. In children over 5 yr of age, postoperative nausea and vomiting was very frequent, with about one-third of the children experiencing this problem. When all events were considered (both major and minor), there was a risk of an adverse event in 35% of the pediatric cases. This contrasts with 17% for adults. This morbidity survey helps to focus on areas of intervention and for further study.

Key Words: ANESTHESIA, PEDIATRIC. COMPLICATIONS, PEDIATRIC.

One of the most frequent questions parents ask of a pediatric anesthesiologist is "What are the risks of anesthesia for my child?" Unfortunately, few studies have examined the consequences of general anesthesia in children. A study from France (1,2) reviewed 40,240 anesthetics administered to children younger than 15 yr of age. There were 27 major complications within 24 h of the administration of the anesthetic (seven per 10,000 anesthetics) (2). However, the study did not elaborate on the morbidity and mortal-

ity associated with children of different age groups for example, neonates. Although the study extended into the recovery period, patient management problems on the ward were not identified. This appears to be the only major morbidity survey of pediatric anesthesia in recent years.

The emergence of quality assurance programs across North America has necessitated the identification of rates and etiologies of patient-related problems. This information is used to improve patient care by the modification of clinical practice; it acts as the justification for resource allocations, and it suggests future research projects. Therefore, there is clearly a need for more information about the implications of anesthetic care in the pediatric population in order to direct and improve future practice.

We were fortunate in having access to the databank from a large anesthesia follow-up program at the Winnipeg Children's Hospital. Data had been collected from mid-1982 to 1987 inclusive (n = 29,220 anesthetics), and we used this information to deter-

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mine the rates of perioperative adverse events occurring in children of different ages.

Methods

The Pediatric Anesthesia Follow-up Program at Winnipeg Children's Hospital is similar to that reported previously for adults and obstetrical cases (3,4). Each child was cared for by a board-certified pediatric anesthesiologist, who filled out a special anesthetic check-off record. This record included information about selected coexisting medical conditions, age of the child, whether the child had a preoperative tour of the hospital, how the airway was managed intraoperatively, and which anesthetic drugs and monitors were used. The anesthesiologist assessed each child preoperatively, categorizing each according to the American Society of Anesthesiologists' physical status classification (5). During the course of anesthesia and surgery, any intraoperative events requiring action by the anesthesiologist were recorded on the same form. Selected adverse events that may have occurred during the immediate recovery period were added to the record by the recovery room nursing staff.

Within 72 h of the procedure, a designated anesthesia follow-up nurse or respiratory therapist reviewed all inpatient anesthesia records for accuracy and completeness and recorded any events the anesthesiologist may have failed to document. All available hospital charts were also reviewed, and any postoperative events were added to the follow-up record. For inpatients, wherever possible, an interview was carried out with the child or parents to learn of any problems and to assess the level of satisfaction or dissatisfaction with the anesthetic experience. The results of the interviews were then added to the record. The complete form was returned to the attending anesthesiologist for review before data processing. As the anesthesiologists' billing card was incorporated into the follow-up record thereby necessitating filling out billing and follow-up information simultaneously, compliance with the program was excellent.

Consistent definitions of the study variables (see Appendix) were used during the 6-yr period, with the exception of two additional variables, added in 1984, relating to airway management. An experienced anesthesia technician familiar with the care of children reviewed 140 random records from the database, comparing the information on the computer files with that of the hospital charts. The information was found to be coded reliably with the exception of

the duration of anesthesia. The data on perioperative events were accurately recorded and thus considered valid for the purpose of this study.

We were first interested in a description of the children and what operations and anesthetic drugs were used. We then determined the rate of adverse events occurring in the perioperative period, namely, (a) during the operative procedure (intraoperative events), (b) immediately postoperatively (recovery room events), and (c) within 3 days of operation (early postoperative events). We expressed the rate of these adverse events per 10,000 anesthetics, with the children divided into five age ranges (under 1 mo, 1–12 mo, 1–5 yr, 6–10 yr, and 11–16 yr). To see if there were time differences in complications, certain analyses were grouped into three time periods: 1982-83, 1984–85, and 1986–87. A χ^2 statistic was used to test for the statistical significance of differences in rates of adverse events across age groups. (Refer to the Appendix for more details on the statistical analysis.) Finally, we compared the overall results for the children with that from our previous study of adults (3) to see if the types and rates of adverse events were similar.

Results

Characteristics of the children in the study are seen in Table 1. The children included neonates to adolescents, with most children in the 1–5-yr age group. The vast majority of the cases were judged to be healthy both in terms of physical status (95% being I or II) and coexisting medical conditions (74% having none). Generally, these children were admitted for elective surgery and increasingly slated as outpatients (45% of cases).

The site of the surgical procedure by age group of the children is found in Table 2. A wide range of procedures were performed at the hospital including intracranial, cardiac, and major vascular. However, the majority of operations were relatively routine "eye, ear, nose, and throat" and musculoskeletal. Neonates had the highest age-specific rates for intracranial, intraabdominal, or major vascular/cardiac procedures.

Details on the anesthetic monitors, drugs used, and duration of anesthesia are found in Table 3. Most of the procedures lasted 15–60 min but 14.3% took more than 2 h. Virtually all children had electrocardiogram, blood pressure, and esophageal stethoscope monitoring as routine procedures; other monitors were modified to particular circumstances. Nitrous oxide was used in 96% of the cases, and

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Table 1. Characteristics of Cases

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Characteristic	n	%
Age		
<1 mo	361	1.2
1–12 mo	2,544	8.7
1–5 yr	13,484	46.2
6–10 yr	7,184	24.6
11+ yr	5,647	19.3
Physical status score		
Ĭ	22,409	76.7
II	5,297	18.1
III	1,237	4.2
IV	205	0.7
V	36	0.1
Elective/emergency status		
Elective	25,940	88.7
Emergency	3,280	11.2
Admission status		
Inpatients	16,137	55.2
Day surgery	13,083	44.8
Time period		
1982–1983	7,280	24.9
1984–1985	10,604	36.2
1986–1987	11,283	38.6
Coexisting medical conditions		
None	21,473	73.6
Upper respiratory	1,724	5.9
Lower respiratory	1,328	4.6
Cardiovascular	831	2.9
Musculoskeletal	1,348	4.6
Metabolic	584	2.0
Renal	340	1.2
On chronic medication	779	2.7
Other conditions	4,427	15.2

halothane was by far the most widely used volatile agent (91%). Use of relaxants for prolonged paralysis was infrequent (9%), although more than half the patients were briefly paralyzed for intubation. We also rarely used diazepam, ketamine, and rectally administered or narcotic agents.

Intraoperative events by age of the child are seen in Table 4. There were considerable differences across the five age groups. Neonates had the highest rate of adverse events, with the most frequent problem being "other respiratory" (laryngospasm, apnea, or bronchospasm). Overall, infants 1–12 mo of age had the fewest intraoperative events when compared with all groups. Among children 1–5 and 6–10 yr of age, the most frequent problems were arrhythmias. The incidence of vomiting and arrhythmia was greater in the older children, whereas difficulties relating to the respiratory system were more frequent in children under 1 yr of age. Mortality rates were the highest in the neonatal group.

Recovery room events are summarized in Table 5. Again, the highest rate of adverse events was seen in the neonatal group. Problems relating to the respira-

tory system were the most frequent, but there were also frequent concerns about temperature changes in these children. In infants 1–12 mo of age, the rate of complications was very low, the most frequent being associated with the respiratory system. Older children (1–5 yr) also had a high incidence of respiratory problems. The adolescent age group had high rates of vomiting as well as respiratory disorders. Again, as for intraoperative events, cardiac arrest was most often seen in the neonatal group.

Table 6 outlines the early postoperative events among children whose charts were reviewed by the nurse (n = 22,760,78% of all anesthetics). About 62% of the neonates had no adverse postoperative events, compared with 81% for infants 1–12 mo and 59% for older children. Among the neonates, the most common problems were respiratory (2519 per 10,000) and cardiovascular (630 per 10,000), whereas in infants 1–12 mo of age, vomiting and problems involving the respiratory system and temperature regulation were common.

A somewhat different picture is seen in older children. The incidence of nausea and vomiting was high for those aged 1–5 yr (20%) and increased in the oldest children to about one in three children. The older children also experienced more sore throats, headaches, and muscle pains, although perhaps these data are misleading, as younger children are unable to express these symptoms. As expected, croup was most frequent in children aged 1–5 yr. Despite the frequency with which these postoperative problems (albeit many minor in nature) occurred, there was very little parental dissatisfaction with the anesthetic experience (about four per 10,000 anesthetics).

As a summary we tabulated in two ways the proportion of cases in which there was at least one perioperative event: first as a function of age group, and second as a function of the year when the procedure was performed. Table 7 gives the final tabulation by age group of the children. Overall, the youngest group (neonates) were the most likely to experience an event intraoperatively or in the recovery room. They were less likely to experience a minor event postoperatively than were the older children but much more likely to undergo a major postoperative event. The rate of having any perioperative event was lowest for infants aged 1-12 mo and highest for children more than 6 yr of age. However, the oldest children were much more likely to experience minor postoperative events considered to be inconveniences but not life-threatening.

For the time-trend summary, about 9% of the cases had at least one event intraoperatively; this trend fell

Table 2. Surgical Site by Age of Child (Percentage of Cases)

			I	Age		
	<1 mo $(n = 361)$	1–12 mo (n = 2,544)	1-5 yr $(n = 13,484)$	6–10 yr (n = 7,184)	11+ yr (n = 5,647)	Total $(n = 29,220)$
Intracranial	3.32	2.52	0.53	0.72	0.74	0.83
EENT	6.65	18.20	52.80	52.34	29.02	44.51
Other head and neck	4.43	8.06	13.36	6.44	6.50	9.76
Intrathoracic nonvascular	6.37	0.67	0.13	0.40	0.66	0.42
Major vascular/cardiac	12.74	1.73	0.59	0.54	0.34	0.78
Intraabdominal	42.11	17.61	3.84	5.58	9.63	7.06
Trunk	5.54	15.80	4.96	4.20	3.67	5.48
Spine	1.66	0.28	0.10	0.28	1.65	0.48
Perineal	4.99	11.36	6.73	5.23	4.66	6.34
Extremities	1.11	11.95	10.38	19.04	35.97	17.48
Endoscopy	8.31	6.13	3.90	4.06	5.68	4.53
Other	2.77	5.70	2.67	1.14	1.49	2.33

EENT, eye, ear, nose, and throat.

Table 3. Anesthetic Drugs, Monitors, and Duration

	n	%
Monitors	***************************************	
Electrocardiogram	29,052	99.4
Blood pressure cuff	28,871	98.8
Precordial/esophageal stethoscope	28,462	97.4
Temperature	13,045	44.6
Nerve stimulator	1,809	6.2
Intraarterial	599	2.0
Urinary catheter	499	1.7
Central venous pressure	438	1.5
Drugs		
Nitrous oxide	27,964	95.7
Barbiturate	6,984	23.9
Muscle relaxant/intubation	14,902	52.1
Muscle relaxant/paralysis	2,630	9.0
Diazepam	88	0.3
Ketamine	321	1.1
Rectal	58	0.2
Local anesthetic	1,782	6.1
Narcotic	2,805	9.6
Halothane	26,619	91.1
Enflurane	789	2.7
Methoxyflurane	88	0.3
Isoflurane	1,753	6.0
Standby	935	3.2
Other drugs	935	3.2
Duration of anesthesia		
<15 min	798	2.7
15–60 min	14,511	49.7
1–2 h	9,744	33.4
>2 h	4,167	14.3

slightly from 1982 to 1987 (Table 8). For recovery-room events, the proportions were very stable over time, at about 13% of cases. Early postoperative events were divided into major and minor, the former being life-threatening or with potential lasting morbidity and the latter more in the nature of incon-

venience. About 21% of the children experienced a minor problem and this decreased from 27.3% in 1982–1983 to 20.9% in 1986–1987. With respect to major postoperative events, about 4% of the children had at least one significant event. Overall, about 40% of the children experienced at least one problem, whether in the intraoperative, recovery-room, or the later postoperative period. This contrasts with the findings in adults who had about the same rate of occurrence of intraoperative events, but much lower recovery and postoperative problems. Overall 18% of the adults had at least one perioperative problem.

Discussion

The Pediatric Anesthesia Follow-up Program database is subject to certain limitations in its ability to assess perioperative events, as discussed in our previous reports (3,4). In our follow-up program, no attempt is made to distinguish adverse events that may be attributable to the surgical procedure rather than to the anesthetic. However, the main focus of the program is to examine consequences of the surgical process that have a high likelihood of an anesthetic contribution. The time frame of the follow-up (72 h) also makes it unlikely that many surgical problems would yet become manifest. The major concerns include the grouping of several outcome variables (for example, "other respiratory" rather than individual events such as laryngospasm or bronchospasm). In addition, the inclusion of an event is subject to interpretation by the individual completing the form, suggesting that what might be considered to be a significant problem by one anesthesiologist may not be considered important by another individ-

Table 4. Intraoperative Events by Age of Child, 1982-1987 (Rate per 10,000 Anesthetics)

						1	Age					
	<1 mo 1–12 mo $(n = 361)$ $(n = 2,544)$				1–5 yr (n = 13,484)		6–10 yr (n = 7,184)		+ yr 5,647)	Total $(n = 29,220)$		
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
None	308	8,532	2,368	9,308	12,585	9,333	6,381	8,882	5,126	9,077	26,736	9,150
Vomiting	1	28	12	47	76	56ª	71	99	77	136°	237	81
Arrhythmia	6	166	22	86	527	391	670	933	317	561	1,542	528^{b}
Blood pressure	14	388ª	14	55	30	22ª	14	19	26	46	99	34
Temperature	3	83	6	24	18	13	6	8	9	16	42	14
Cardiac arrest	1	28	3	12	4	3	3	4	3	5	14	5
Airway obstruction	8	222	51	200°	133	99	62	86	51	90	305	105
Other respiratory	26	720°	81	318^{a}	159	118	59	82ª	56	99	381	130
Drug incident	0		5	20	27	20	20	28	20	35	72	25
Surgical	1	28	8	31	53	39	31	43	22	39	115	39
Death	3	83ª	2	8	4	3	1	1	1	2	11	4

 $^{^{}a}P$ < 0.01, exact tail probability calculation based on Poisson distribution.

Table 5. Recovery Room Events by Age of Child, 1982-1987 (Rate per 10,000 Anesthetics)

						1	Age					
	(n :	1 mo = 361)	1-12 mo $(n = 2,544)$			i yr 3,484)		0 yr 7,184)	11 + yr $(n = 5,647)$		Total $(n = 29,220)$	
	п	Rate	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
None	301	8,338	2,376	9,340	11,971	8,878	6,201	8,632	4,848	8,585	25,696	8,794
Laryngospasm	1	28	11	43	252	187	127	177	93	165	484	166ª
Vomiting	0		21	83	552	410	614	855	528	935	1,715	587ª
Cardiac arrest	2	55^{b}	1	4	3	2	1	1	0		7	2
Arrhythmia	0		3	12	11	8	11	15	5	9	30	10
Blood pressure	50	$1,385^{b}$	3	12	13	10^{b}	11	15^{b}	18	32	95	17
Temperature	17	471 ^b	35	138	77	57^{b}	62	86	90	159 ⁵	281	96
Airway obstruction	1	28	41	161	599	444	187	260	104	184	932	319^{a}
Other respiratory	42	$1,163^{b}$	63	248^{b}	142	105	56	78^{b}	58	103	361	124
Drug incident	0	•	5	20	26	19	14	19	17	30	62	21
Surgical	1	28	16	63	177	131	120	167	43	76	357	122

 $^{^{}a}P < 0.01$, χ^{2} test for association.

ual. However, as the follow-up reviewer examines all records and the majority of hospital charts, it is unlikely that any major events would have been missed. There is still the possibility that the more minor adverse events may have been underreported.

During the creation of the form in the mid-1970s, the most important perioperative events were included in the check-off format based on what was then considered to be the major concerns for children undergoing anesthesia. Thus the form may not reflect more current knowledge about pediatric anesthesia nor the recent introduction of monitors or therapeutic agents. In addition, the change in follow-up personnel during the study period is of concern, particularly when recording events with a large subjective component such as parental dissatisfaction. However, the consistency in the rates over the 6-yr period makes it

unlikely that there was a major problem with interobserver reliability.

Children less than 1 mo old appeared to have the greatest risk of perioperative adverse events, particularly major problems such as cardiac arrest and other cardiovascular or renal events. Perioperative death rates were also higher for these children. However, in view of the small number of children in this age group coming to operation, the influence of one or two adverse events on such occurrence rates can be dramatic. These infants were also much more likely to undergo major surgical procedures (i.e., cardiovascular or intraabdominal) and were more likely to be assessed preoperatively as PS 3 to PS 5 than the older children. In addition, these infants were routinely nursed in the Intensive Care Nursery where the greater level of observation in the imme-

 $[^]bP < 0.01$, χ^2 test for association.

 $^{^{}b}P < 0.01$, exact tail probability calculation based on Poisson distribution.

Table 6. Early Postoperative Events by Age of Child (Rate per 10,000 Charts Reviewed)

						1	Age				_	
		1 mo = 270)	-	2 mo 2,045)		5 yr 10,158)		.0 yr 5,693)		+ yr 4,594)	To (n = 2	
	n	Rate	n	Rate	n	Rate	n	Rate	'n	Rate	n	Rate
None	167	6,185	1,656	8,098	7,341	7,227	3,392	5,958	2,690	5,855	15,247	6,699
Nausea/vomiting	13	481	100	489	2,042	2,011	1,949	3,424	1,474	3,209	5,579	2,4514
Other respiratory	68	2,519	121	592	196	196	81	142	82	178	548	241ª
Temperature	20	741	77	377	226	222	111	195	97	211	531	233a
Surgical	1	37	53	259	183	180	122	214	70	152	429	188ª
Other problem	3	111	51	249^{b}	172	169	78	137	73	159	377	166
Croup	2	74	22	108	135	133^{b}	27	47^b	13	28^{b}	199	87
Cardiovascular	17	630^{b}	24	117^{b}	30	30^{b}	28	49	20	44	119	52
Positional	1	37	4	20	28	28	23	40	26	57	82	36
Renal	6	222^{b}	6	29	23	23	14	25	24	52	73	32
Eye	1	37	6	29	25	25	4	7^b	13	28	49	22
Arterial line	4	148^{b}	10	49^{b}	12	12	6	11	9	20	41	18
Behavior disorder	1	37	6	29	18	18	5	9	5	11	35	15
Thrombophlebitis	5	185^{b}	4	20	5	5	4	7	9	20	27	12
Seizures	1	37	3	15	6	6	7	12	0		17	7
Parental dissatisfaction	0		1	5	3	3	1	2	3	7	8	4
Death	4	148^{b}	1	5	2	2	1	2	2	4	10	4
Hepatic	0		0		0		0		0		0	0
Nerve palsy	0		0		0		0		0		0	0
Sore throat	c		c		44	43	99	174	145	316	289	141^d
Headache	c		c		42	41	66	116	134	292	242	118^{d}
Muscular pain	c		с		33	32	36	63	59	128	128	56^{d}
Dental	c		1	5	4	4	8	14	4	9	17	8
Awareness	c		c		2	2	7	12	3	7	12	5

[&]quot;P < 0.01, χ^2 test for association, 2 × 5 contingency table.

Table 7. Perioperative Events, Summary by Age Group (Percent Total Anesthetics)

	<1 mo $(n = 361)$	1-12 mo $(n = 2,544)$	1-5 yr $(n = 13,484)$	6-10 yr $(n = 7,184)$	11 + yr $(n = 5,647)$
Any intraoperative event	14.96	7.31	7.10	12.22	9.69
Any recovery-room event	16.61	7.23	12.20	14.88	15.23
Any postoperative					
Minor event"	13.57	10.30	20.32	31.49	32.44
Major event ^b	23.82	7.51	3.26	3.37	3.33
Any evente					
Among patients seen	48.89	25.92	37.50	50.52	51.33
Among all patients	41.55	23.47	33.16	45.04	45.78

[&]quot;Includes nausea and vomiting, sore throat, muscle pain, headache, dental, positional, extremities, eye, croup, temperature, behavior problem, thrombophlebitis, arterial line problem, awareness, and "other."

b'Includes "other respiratory," cardiovascular, nerve palsy, hepatic, renal, seizures, surgical complications, and death.

diate postoperative period may result in an enhanced detection of perioperative events. As a result of this study, we have reviewed our management of neonates. Specifically, we identified significant problems with hypothermia and cardiovascular instability during transportation of ill neonates weighing less than 1000 g from the intensive care nursery, which is located on a different floor, to the operating rooms. Currently, we administer general anesthesia in the nursery for the most critically ill neonates rather than expose them to the risks of transport. Because of the higher incidence of major events in neonates, we have extensively reviewed our monitoring requirements for neonates. Our major conclusion is that there is an increasing need for equipment suppliers to design anesthesia monitors and ventilators specifi-

^bP < 0.01, exact tail probability calculation based on Poisson distribution.

^{&#}x27;Children under the age of 1 yr could not describe these symptoms.

 $[^]dP < 0.01$, χ^2 test for association, 2 × 3 contingency table.

Percentage of total anesthetics in which there was at least one event in either the intraoperative, recovery-room, or later postoperative period.

Table 8. Perioperative Events Summary Over Time (% Total Anesthetics)

	C	5)	Adults ^a (%)	
	1982–83	1984-85	198687	1979-83
Any intraoperative	9.52	9.00	8.58	10.6
Any recovery room	12.91	13.24	13.03	5.9
Any postoperative				
Minor ^b	27.38	26.21	20.86	9.4
Major ^c	3.82	4.39	3.55	0.5
Any event ^d				
Ámong cases seen	44.58	42.95	40.82	31.6
Among all cases	40.23	38.61	35.35	17.8

"Reference 3.

cardiovascular, nerve palsy, hepatic, renal, seizures, surgical, and death.

Percentage of total anesthetics in which there was at least one event in either the intraoperative, recovery-room, or later postoperative period.

cally for the intraoperative management of very small neonates.

With regard to intraoperative events, there was little difference between the rate of adverse events for the pediatric age group as compared with the rates for adults (3). In the adult group, the overall rate of any intraoperative complication was 10.6 per 10,000 and in children was about nine per 10,000. In the recovery room, the profile of adverse events experienced by the children differed considerably from that of the adults: children were less likely to experience problems with arrhythmias or hypotension, but were more likely to have problems related to the respiratory system. Overall the rate of recovery room complications was 5.9 per 10,000 for adults and 13 per 10,000 for children. These results formed the administrative rationale for the purchase of additional monitoring equipment such as oximetry and noninvasive blood pressure machines for the recovery room.

Among the older children, there was a considerable problem with postoperative nausea and vomiting, with nearly one-third of the children experiencing this problem. This is in contrast to only 5% of adults with the same complaint (3). As with the adult patients, nausea and vomiting were the most frequent postoperative problems in this study. However, the low rate of administration of intraoperative narcotics in the pediatric population (as compared with the adults we studied) suggests an etiology distinct from the anesthetic drugs, perhaps including the surgical procedure itself, anxiety, fear, or postoperative pain. In an effort to reduce postoperative nausea, we have significantly increased our use of supplemental regional anesthesia among other measures.

As noted above, there are no large series with which to compare the present results with the exception of that of Tiret et al. from France (2). However, comparisons between the two series are difficult because of differences in patient populations, surgical profiles (e.g., eye, ear, nose, and throat procedures constituted 30.9% of the French series compared with 44.5% in ours), duration of follow-up (the French study included only events occurring within 24 h of the procedure, whereas our study extended to 72 h postoperatively), and definitions of outcomes. One comparison that can be made is that of the rate of cardiac arrest: in the French study, the rate of cardiac arrest for infants under 1 yr of age was 19 per 10,000 anesthetics, which compares favorably with the present study rate of 24 per 10,000. An interesting point was that in the French study, there were no major events in children undergoing cardiac procedures.

In evaluating the findings of this survey, we can see that children's experience with anesthesia is quite different from that of adults. Not only are the types of problems dissimilar, but the timing of the disorders extend well into the postoperative period. Whereas the profile of problems is probably not that surprising, the magnitude of the occurrence rates is noteworthy. This study has certainly prompted us to be more vigilant in assessing the respiratory system in children.

We were pleased that there was a stability or, in the case of postoperative events, a decline in the rate of problems over time. The number of deaths was too small to show time trends, but the decrease in morbidity is encouraging. We found that this audit was particularly helpful in assessing the quality of care at our institution, and it has led to modifications in patient care. By defining the problems, prophylactic measures such as alternative methods of pain control, respiratory management, and antinausea therapy can be implemented and evaluated. Although observations such as these cannot be generalized to other hospitals, they do point out the merit of monitoring perioperative events in directing future therapeutic

In summary, we have carried out a survey of 6 yr of experience with pediatric anesthesia at our hospital. This paper highlights the differences between children and adults especially in three areas: the high morbidity rate among neonates, the importance of respiratory disorders in younger children, and the high frequency of postoperative nausea and vomiting in older children. These areas require attention in designating areas for future investigation and intervention.

^bIncludes nausea and vomiting, sore throat, muscle pain, headache, dental, positional, extremities, eye, croup, temperature, behavior problem, thrombophlebitis, arterial line problem, awareness, and "other." Includes "other respiratory," cardiovascular, nerve pals

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Appendix

A. Definition of Variables Used in the Follow-up Study

Coexisting medical conditions: Upper respiratory—upper respiratory illness or difficult airway; Lower respiratory—includes asthma, cystic fibrosis; Metabolic—includes diabetes and thyroid disorcers; Receiving chronic medications—includes bronchodilators and anticonvulsants; Other conditions—includes neurologic and hematologic disorders.

Intraoperative events: Arrhythmia—includes supraventricular, ventricular, or heart block; Blood pressure—hypotension where blood pressure fell at least 30% from preoperative value; Temperature—hypothermia; Other respiratory—includes laryngospasm and bronchospasm; Drug incident—anaphylactoid reactions or other drug reactions; Surgical—mainly excessive bleeding.

Recovery-room events: Same definitions as for intraoperative.

Postoperative events: Muscular pain—generalized (fasiculation) muscle pain; Dental—broken or chipped teeth; Positional—pain, bruising, or pressure sores in localized area possibly due to malpositioning during the procedure; Eye—corneal abrasion, conjunctivitis; Other respiratory—atelectasis, pulmonary edema, pneumonia; Temperature—elevated temperature greater than 38°C; Cardiovascular—hypotension, hypertension, arrhythmia, tachycardia, bradycardia; Hepatic—jaundice; Renal—oliguria; Arterial line—excessive bruising, no pulse; Awareness—recall of events in the operating room; Surgical—excessive bleeding, return to operating room.

B. Statistical Methods

As the number of infants less than 1 mo old was small (n = 361), a χ^2 test was not suitable for determining differences across age groups for many of the

variables occurring at low rates. Therefore, to test for statistically significant equalities among the remaining variables in rates of outcomes across the five age groups, we compared the rate for each adverse event for a specific age group with that of the rate for all ages. This was done by comparing the observed number of events with the expected number of events (standardized morbidity ratio [SMR]). The age-specific expected number of events was determined by multiplying the number of children in each age strata by the observed rate of occurrence of each event in the total sample. The statistical significance of the SMR was assessed by calculating the exact tail probability of the Poisson distribution for observing more (for SMR > 1) or less (for SMR < 1) events than expected. To account for multiple statistical comparisons *P* values <0.01 were considered to be indicative of statistical significance.

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Intrathecal Morphine Dose-Response Data for Pain Relief After Cholecystectomy

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YAMAGUCHI H, WATANABE S, MOTOKAWA K, ISHIZAWA Y. Intrathecal morphine dose-response data for pain relief after cholecystectomy. Anesth Analg 1990;70:168–71.

We studied the effect of low-dose intrathecal morphine (0.00–0.20 mg) on pain relief and the incidence of side effects after cholecystectomy in 139 patients divided into eight groups according to intrathecal morphine dose: groups 1 (0.00 mg), 2 (0.04 mg), 3 (0.06 mg), 4 (0.08 mg), 5 (0.10 mg), 6 (0.12 mg), 7 (0.15 mg), and 8 (0.20 mg). Preservative-free morphine hydrochloride mixed in hyperbaric tetracaine solution was administered at the time of induction of spinal anesthesia just before surgery. Pain relief was significantly greater for the first 24 h in groups 3, 4, 5, 6,

7, and 8 than in group 1. The incidence of respiratory depression was significantly greater in groups 7 and 8 than in the other groups in the first 48 h. Vomiting occurred significantly more often in group 1 than in groups 2, 3, 4, and 5. Intraoperative cholangiography and the postoperative clinical course indicated no increase in tone of the sphincter of Oddi in any patient. We conclude that 0.06–0.12-mg intrathecal morphine is the best dose range for pain relief after cholecystectomy without respiratory depression and with the lowest incidence of vomiting or pruritus, or both.

Key Words: PAIN, POSTOPERATIVE. ANALGESICS, MORPHINE. ANESTHETIC TECHNIQUES, SPINAL—morphine.

Intrathecal morphine for postoperative relief of pain often may be accompanied by side effects such as nausea, vomiting, urinary retention, pruritus, and potentially life-threatening and delayed respiratory depression (1–6). Side effects cannot always be reliably predicted in advance (7–10), and respiratory depression appears to be related in part to the amount of morphine injected intrathecally. The doseresponse relationships for intrathecal morphine in the management of pain, especially in the low-dose range, however, have not been well established.

Previously, we reported that in the dose range of 0.04–0.08 mg, intrathecal morphine relieved postoperative pain for as long as 24 h after transabdominal hysterectomy in 60%–70% of the patients (11). In the present study, we prospectively investigated the analgesic efficacy of intrathecal morphine and the incidence of side effects when given in the dose range of

0.00–0.20 mg to patients undergoing cholecystectomy.

Materials and Methods

We studied 160 patients, ASA physical status I or II, scheduled for elective cholecystectomy for cholelithiasis between October 1984 and December 1987 at the Mito Saiseikai General Hospital. The research protocol was approved by the hospital ethical committee. At the time of preanesthetic assessment, patients were consecutively assigned to a step-up dose schedule starting with 0.00 mg, progressing to 0.04, 0.06, 0.08, 0.10, 0.12, 0.15 mg, and ending with 0.20 mg of intrathecal morphine injected at the time of induction of spinal anesthesia for the proposed surgery (Table 1). This was repeated until 160 patients were obtained. Patients in whom surgery was canceled, who were given preoperative opiates or other analgesics, or who had preoperative nausea or vomiting were excluded from the study and the scheduled doses were skipped. Written informed consent was obtained from each patient.

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Table 1. Patient Data

Variable	Group							
	1	2	3	4	5	6	7	8
No. of patients	20	16	16	19	19	17	15	17
(Male/female)	8/12	7/9	7/9	8/11	12/7	9/8	4/11	8/9
Morphine dose (mg)	0.00	0.04	0.06	0.08	0.10	0.12	0.15	0.20
Age (yr)	53 ± 15	53 ± 7	58 ± 11	55 ± 14	54 ± 13	62 ± 11	53 ± 9	56 ± 13
Height (cm)	155 ± 8	158 ± 11	157 ± 7	155 ± 5	159 ± 9	156 ± 7	153 ± 13	158 ± 10
Weight (kg)	57 ± 9	59 ± 11	55 ± 9	59 ± 9	60 ± 9	56 ± 8	55 ± 9	58 ± 11
Duration (h)	1.6 ± 0.6	1.3 ± 0.5	1.5 ± 0.9	1.4 ± 0.6	1.4 ± 0.5	2.0 ± 0.9	1.9 ± 0.6	1.8 ± 0.7

Data are mean ± sp.

No significant differences among the eight groups.

Duration = duration of surgery.

All patients were premedicated with 1.0 mg of oral flunitrazepam 90 min before entering the operating theater. Intrathecal injections (in total volumes of 2.6-3.2 mL) consisted of 14-16 mg of tetracaine hydrochloride and preservative-free morphine hydrochloride (0.00-0.20 mg) in 10% glucose. In the right lateral decubitus position, lumbar tap was performed with a 23-gauge spinal needle at L2-3 intervertebral space; the spinal mixture was injected at a rate of 0.2 mL/s and the patient was turned to the supine horizontal position. General anesthesia was then intravenously induced with 5 mg/kg of thiopental, followed by tracheal intubation that was facilitated by succinylcholine (1 mg/kg IV). General anesthesia was maintained using 0.5%–1.0% enflurane, 67% nitrous oxide, and oxygen. During surgery, no intravenous analgesics were given. After tracheal extubation, the patients were returned to the ward rooms.

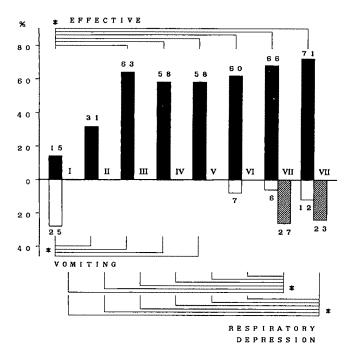
For the first 48 h after the intrathecal injection, heart rate and respiratory rate, using a thoracic impedance detector incorporated in the electrocardiogram electrodes, were continuously monitored (Life Scope 11, Nihon Kohden, Tokyo, Japan). The following observations and recordings were made by ward nurses not informed of the intrathecal morphine doses: (a) time at which analgesics were first requested and given for relief of wound pain regardless of intensity, (b) respiratory rate per minute, and (c) patient vomiting and/or complaint of pruritus. On the first postoperative day, each patient was asked whether colic abdominal pain had occurred. To evaluate respiratory depression, the right radial artery was punctured and blood was drawn for Paco₂ determination when (a) respiratory rate was less than 10 times per minute, (b) response to verbal commands was poor, and (c) 5-8 h had passed since intrathecal injection of morphine. If Paco₂ was above 50 mm Hg, arterial blood gas analysis was repeated every 2-4 h up to 20 h after surgery. The incidence of urinary retention could not be evaluated because urethral catheters were in place during and after surgery.

In patients who requested no analgesics during the first 24 h, pain relief was considered "effective." Patients who vomited during the first 48 h were labeled as "vomiting." Patients with a respiratory rate 10 times or less per minute and/or with a Paco₂ of 50 mm Hg or more on one or more occasions were considered to have experienced respiratory depression. The percentages of patients categorized as having effective pain relief, respiratory depression, and vomiting were calculated for each group.

Patient data were analyzed by analysis of variance, followed by Bonferroni's correction of the t-test. The differences among the eight groups regarding the categories "effective," "respiratory depression," and "vomiting" were analyzed by χ^2 test followed by Bonferroni's correction. P values less than 0.05 were considered statistically significant.

Results

One patient each from groups 2, 3, 4, 5, and 8 and two patients each from groups 6 and 7 were excluded because the proposed surgery was not subsequently carried out. In addition, two patients each from groups 3 and 8 and one patient each from groups 2, 6, and 7 were excluded because they were given analgesics and/or antiemetics before surgery. Finally, two patients from group 2, one patient from group 3, and two patients from group 7 were excluded from the study because they were given antiemetics for nausea during the first 48 h. We then analyzed the data of the remaining 139 patients among the eight groups. There were no significant differences in mean age, height, weight, and duration of surgery (Table 1). Five minutes after the injection of the spinal mixture, the cephalad level of analgesia was T4-6 by pin-prick. During surgery, no unusual events occurred.



<u>Figure 1</u>. Percentages of patients classified as having effective relief of postoperative pain in first 24 h (*closed bar*), as vomiting (*open bar*), and as respiratory depression (*hatched bar*). *Significant difference, P < 0.05.

Figure 1 shows the percentages of "effective," "respiratory depression," and "vomiting." The percentages of "effective" were significantly greater in groups 3 (0.06 mg), 4 (0.08 mg), 5 (0.10 mg), 6 (0.12 mg), 7 (0.15 mg), and 8 (0.20 mg) than in group 1 (0.00 mg). There were no statistically significant differences in postoperative pain between groups 1 and 2 (0.04 mg), or between groups 2, 3, 4, 5, 6, 7, and 8.

Respiratory depression was observed in four patients in group 7 and in four patients in group 8. All eight patients developed $Paco_2$ levels above 50 mm Hg, often with poor responses to verbal commands, with 58 mm Hg as the maximum. These increased $Paco_2$ levels lasted 12-16 h without further elevation of $Paco_2$ level or further depression of poorer responses to verbal commands. Three patients developed respiratory rates of seven, nine, and nine times per minute, respectively, but none of them developed poor responses to verbal commands. Six of these eight patients were classified as having effective relief of postoperative pain. The incidence of respiratory depression in groups 7 and 8 was significantly greater than in any other group (P < 0.05, Figure 1).

The incidence of vomiting in group 1 was significantly greater than in groups 2, 3, 4, 5, and 6. There were no significant differences in the frequency of vomiting among groups 1, 7, and 8, or between groups 2, 3, 4, 5, and 6. All five patients in group 1 who vomited required analgesics, whereas both of

the two "vomiting" patients in group 8 were classified as having the effective pain relief. The difference in the percentages of patients who vomited and required analgesics between groups 1 and 8 was significant (P < 0.01).

Two patients complained of general pruritus (one with and one without effective pain relief in groups 7 and 8, respectively). Pruritus was not related to dose of morphine injected intrathecally.

Intraoperative cholangiograms made about 1 h after the intrathecal injection showed no significant constriction of the sphincter of Oddi, and a postoperative interview revealed that no patient complained of colic abdominal pain suggestive of spasm of the sphincter of Oddi.

Discussion

There are many reports of intrathecal administration of morphine for postoperative pain relief (2,3,11–20). We previously reported that the minimal effective intrathecal morphine dose for pain relief after transabdominal hysterectomy was 0.04 mg (11)—the lowest reported effective dose. In the present study, the minimal dose of intrathecal morphine that effectively relieved pain after cholecystectomy for the first 24 h was 0.06 mg. We attribute the dose difference to differences in the site and type of surgical procedure.

In the present study, the incidence of postoperative wound pain was calculated using the number of patients who requested and were given analgesics for incisional pain during the first 48 h, regardless of the intensity, which is our routine practice (11). Fifty-eight percent to 71% efficacy, however, is not adequate from the clinical point of view. Therefore, we recommend that supplement analgesics be given when necessary to achieve a satisfactory level of postoperative analgesia.

Regarding the method of detecting respiratory depression, we continuously monitored respiratory rate and performed arterial blood gas analysis 5–8 h after morphine administration, a period that was previously known to be "the most probable time of clinical manifestation" of respiratory depression (7).

Side effects such as delayed-onset respiratory depression, nausea, vomiting, urinary retention, and pruritus have often been accompanied by doses of intrathecal morphine as small as 0.25 mg (1,2). The respiratory depression in the present study could be attributed to intrathecal morphine itself, because the incidence was significantly higher in patients given 0.15 and 0.20 mg of morphine intrathecally than in patients given lesser dosages, and because six of the

eight patients with respiratory depression were patients whose pain was effectively relieved. We emphasize that respiratory depression can occur with a dose of intrathecal morphine as small as 0.15 mg.

The effective dose of epidurally administered morphine for the relief of postoperative pain has been reported to range from 2 to 8 mg (15,21–23). No more than 2% (24) or 4% (25) of morphine epidurally administered is available in cerebrospinal fluid, and intrathecal morphine doses for postoperative pain relief are 10–16 times less than doses required for epidural administration (20). These data agree with the present results.

In our previous study (11), we reported that the incidence of vomiting was significantly greater in patients given 0.10 mg of intrathecal morphine than in those given smaller doses. In the present study, we observed some instances of vomiting in patients given 0.12, 0.15, and 0.20 mg of morphine intrathecally, but the incidence was low and not significant clinically. We attribute the difference in the incidence of vomiting in the two studies to the different surgical procedures, not to the dose of intrathecal morphine itself.

Systemic narcotics may precipitate spasm of the sphincter of Oddi. There is no report that intrathecal opioids increase the sphincter tone. In the present study, the intraoperative cholangiogram after cholecystectomy revealed no abnormal findings suggestive of spastic constriction of either the common bile duct or the sphincter of Oddi. In addition, the postoperative clinical courses of our patients were uneventful and no patients complained of colic abdominal pain indicative of biliary tract spasm.

In conclusion, the intrathecal administration of morphine hydrochloride in the dose range of 0.06–0.12 mg mixed in hyperbaric tetracaine solution made postoperative analysesics unnecessary in about 60% of the patients for the first 24 h after cholecystectomy and was virtually free from the incidence of the side effects associated with intrathecal morphine.

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Succinylcholine Does Not Increase Serum Potassium Levels in Patients With Acutely Ruptured Cerebral Aneurysms

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MANNINEN PH, MAHENDRAN B, GELB AW, MERCHANT RN. Succinylcholine does not increase serum potassium levels in patients with acutely ruptured cerebral aneurysms. Anesth Analg 1990;70:172–5.

Succinylcholine-induced hyperkalemia has been reported to occur in many neurological disorders including subarachnoid hemorrhage. The purpose of this study was to compare the effect of succinylcholine on serum potassium levels in patients with ruptured cerebral aneurysms undergoing either early (≤ 4 days; n=14) or delayed (5-16 days; n=20) surgery. Thirty-four patients were classified according to the number of days from subarachnoid hemorrhage to surgery. Arterial serum potassium levels were measured after induction of anesthesia but before succinylcholine, and

1, 5, and 10 min after the administration of succinylcholine. The electrocardiogram was continuously monitored. The mean $(\pm sD)$ increase in serum potassium level of 0.4 ± 0.2 mmol/L occurred at 10 min but was not statistically significant, nor was there any statistically significant difference in serum potassium levels related to time between subarachnoid hemorrhage and administration of succinylcholine. We found no evidence of succinylcholine-induced hyperkalemia in patients undergoing either early or delayed cerebral aneurysm surgery.

Key Words: ANESTHESIA, NEUROSURGICAL. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE. IONS, POTASSIUM.

The administration of succinylcholine to normal individuals may result in an increase of the serum potassium levels averaging 0.5 mmol/L (1). Marked hyperkalemia after administration of succinylcholine has been reported in a number of conditions including burns, trauma, and neurological disorders such as peripheral neuropathies, cerebral vascular accidents, and head and spinal cord injury (2-4). Succinylcholine-induced hyperkalemia has also been reported in patients with ruptured cerebral aneurysms (5,6). Recent neurosurgical practice is to operate on patients early after subarachnoid hemorrhage (SAH), that is, within 72 h of the bleed (7). The purpose of this study was to investigate the effects of succinylcholine on serum potassium levels in patients during surgical treatment of ruptured cerebral aneurysms and to compare levels in patients undergoing early surgical treatment with those in patients undergoing delayed surgery.

Methods

This study was approved by the Health Sciences Standing Committee on Human Research for the University of Western Ontario. Informed consent was obtained from 34 patients undergoing cerebral aneurysm surgery. Patients were classified according to the number of days after their SAH to the time of administration of succinylcholine (Table 1). The presence and duration of any preoperative neurological deficits were documented.

All patients were unpremedicated. After sedation with a narcotic and infiltration with local anesthesia, an intraarterial catheter was inserted into the radial artery. Anesthesia was then induced with 3–5 μ g/kg fentanyl (n=26) or 0.5–1 μ g/kg sufentanil (n=8) plus, in both instances, 4–6 mg/kg thiopental and 1.0 mg/kg lidocaine. In 22 patients, 1.0 mg/kg succinylcholine was administered to facilitate tracheal intubation. Because of the preference of the anesthetist, 12 patients received 0.04 mg/kg d-tubocurarine at the beginning of induction and the succinylcholine dose was increased to 2 mg/kg. After intubation, patients were mechanically ventilated to maintain end-tidal CO_2 between 32 and 35 mm Hg. Anesthesia was

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Table 1. Patient Classification

Timing of surgery	Group	Days from SAH	Number of patients
Early	1	≤2	8
•	2	3-4	6
Delayed	3	5–9	5
	4	10-15	9
	5	≥16	6

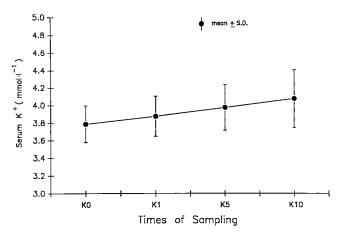
SAH, subarachnoid hemorrhage.

maintained with air/oxygen and isoflurane. A lead-II electrocardiogram was continuously monitored and any changes in rate, rhythm, and configuration of the T wave were documented. Blood samples were withdrawn from the arterial catheter for measurements of serum potassium levels at the following times: K_0 , immediately before induction of anesthesia, and K_1 , 1 min, K_5 , 5 min, and K_{10} , 10 min after succinylcholine administration. Serum potassium levels were measured by an ion-selective electrode (Beckman Autoanalyzer) with low- and high-quality controls each testing. Arterial blood gas tensions were measured at K_0 and K_{10} . In 15 patients, two further arterial samples for serum potassium measurements were obtained 15 and 20 min after succinylcholine administration. Statistical analysis was performed using analysis of variance with repeated measures and Dunnett's test. A P value of <0.05 was considered statistically significant.

Results

No anesthetic-related complications occurred during the study. The mean (\pm sD) age of the patients was 50 \pm 12 yr (20 women, 14 men). Mean weight was 71 \pm 13 kg. Six patients had preoperative neurological deficits (either hemiparesis or hemiplegia). The duration of the preoperative neurological deficits ranged from 2 to 45 days.

Mean (\pm sD) serum potassium levels in all 34 patients increased from 3.8 ± 0.4 to 4.1 ± 0.5 mmol/L 10 min after succinylcholine administration, that is, a mean increase of 0.4 ± 0.2 mmol/L (Figure 1). This was not a statistically significant increase. The greatest increase in any individual patient was 0.8 mmol/L 10 min after succinylcholine administration. This magnitude of an increase occurred in three patients, none of whom had preoperative neurological deficits. In the 15 patients who had samples drawn at 15 and 20 min, there was no further increase in serum potassium levels after the 10-min sample. Figure 2 shows the serum potassium levels in all patients



<u>Figure 1</u>. Serum potassium levels (mean \pm sp) in all patients at K_0 (before succinylcholine), and K_1 (1 min), K_5 (5 min), and K_{10} (10 min) after succinylcholine. The mean increase (0.4 mmol/L) was not statistically significant.

divided by the number of days following their SAH. There was no statistically significant difference in the serum potassium level between the groups at any time of sampling or within each group at all times of sampling.

The mean pH and Paco₂ values before succinylcholine administration were 7.37 \pm 0.05 and 40 \pm 8 mm Hg, and at 10 min 7.4 ± 0.04 and 35 ± 6 mm Hg, respectively. These differences were not statistically significant. The 12 patients who had a precurarizing dose of d-tubocurarine had a mean ($\pm sD$) increase in serum potassium levels of 0.3 ± 0.2 mmol/L compared with an increase of 0.5 ± 0.3 mmol/L in patients who did not receive d-tubocurarine. This difference was not statistically significant. The six patients who had a neurological deficit preoperatively did not show any greater increase in serum potassium levels than did patients who had no deficits. Electrocardiographic monitoring showed no change in rhythm or of the T wave. There were no untoward cardiovascular events during the study period.

Discussion

In contrast to previous reports of succinylcholine-induced hyperkalemia in patients with ruptured cerebral aneurysms, we were unable to demonstrate this finding in our study. Thomas (5) reported a case of cardiovascular collapse after succinylcholine administration that was associated with hyperkalemia in a patient with a ruptured cerebral aneurysm. This patient received succinylcholine for tracheal intubation without any ill effect 3 days after SAH. It was not until day 34 after a difficult postoperative course,

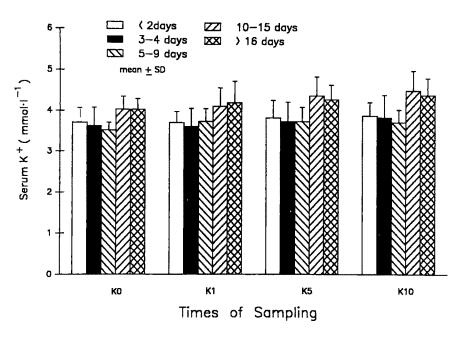


Figure 2. Serum potassium levels divided according to the number of days between SAH and surgery. There was no statistically significant difference either between groups or within each group at all times of sampling.

including the development of quadriplegia, that the patient had a cardiovascular collapse associated with the use of succinylcholine. This occurred again at day 36, at which time an arterial blood sample showed a potassium level of 7.3 mmol/L. Thus, this report illustrates the hyperkalemic response of a patient with prolonged major neurological deficits.

Iwatsuki et al. (6) studied 22 patients with ruptured cerebral aneurysms undergoing surgical treatment. They found a statistically significant mean increase of 1.4 ± 0.3 mmol/L in serum potassium level at 1 min after succinylcholine administration. The maximum increase in their study of any individual patient was 6.1 mmol/L. The mean maximum increase in our study was 0.4 mmol/L, which is comparable to the expected rise in the normal population (1). The patient population in Iwatsuki's study differed from ours in that they had more patients who had delayed surgery in comparison to our study where a larger number had early surgery, but there was no difference in the number or duration of the neurological deficits preoperatively. Iwatsuki et al. were unable to explain the reason for the hyperkalemia as even the patients who did not have a neurological deficit developed hyperkalemia. In their study the patients who developed potassium levels >6 mmol/L had surgery that was delayed from 10 to 50 days after SAH, but they found no relationship between the increase in potassium and the severity of loss of consciousness with SAH, or with the presence of neurological deficits. They speculated that the other factor that may contribute to the hyperkalemic response is subarachnoid blood, as patients who have brain lesions such as tumors, not associated with bleeding, do not develop a hyperkalemic reaction to succinylcholine (8). If the presence of blood in the cerebrospinal fluid has any influence on the effect of succinylcholine on potassium release, we would have expected the patients undergoing early surgery to show a greater increase in potassium. We found no difference in patients undergoing early surgery compared with those undergoing delayed surgery.

Anesthesic induction agents may modify the slight increase in serum potassium level normally seen after succinylcholine administration. Thiopental decreases the initial increase in serum potassium more than other agents such as halothane (9,10). Perhaps the thiopental used in our study did offer some protection after succinylcholine, although Iwatsuki also used thiopental for induction, yet found a significant increase in serum potassium levels at 1 min. d-Tubocurarine may also attenuate the hyperkalemic response to succinylcholine, but this protection is not consistent (11,12). β -Adrenoceptor blockers may modify the release of potassium after succinylcholine. β -Blockers have been shown in dogs to augment and prolong the increase in serum potassium, but in human studies to attenuate the increase (13,14). Five patients in our study were taking a β -adrenoceptor blocker preoperatively for the treatment of hypertension. These patients showed no significant difference from patients not receiving β -blockers in their response to succinylcholine.

The number of patients with neurological deficits in our study was small, and only three patients had deficits that were present for more than 10 days after SAH; thus we cannot make any conclusion on the SUCCINYLCHOLINE AND SAH

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effect of succinylcholine on serum potassium levels in the presence of prolonged neurological deficits.

In conclusion, we found no significant increase in serum potassium levels in patients undergoing cerebral aneurysm surgery at any time after administration of succinylcholine. Patients undergoing early surgery after SAH are not at an increased risk for the development of succinylcholine-induced hyperkalemia.

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Preoperative Laboratory Testing of Children Undergoing Elective Surgery

Mary E. O'Connor, MD, MPH and Kenneth Drasner, MD

O'CONNOR ME, DRASNER K. Preoperative laboratory testing of children undergoing elective surgery. Anesth Analg 1990;70:176–80.

The routine preoperative evaluation of pediatric patients often includes a history, physical examination, complete blood count, and urinalysis (UA). We retrospectively reviewed the records of 486 elective surgeries in children to determine the role of abnormal preoperative laboratory test results in perioperative management. Anemia or microcytosis was apparent in 17% of patients, and abnormal UA results were found in 15%. More than 80% of the abnormal UA results were historically known, clinically insignificant, or false-positives.

Only five children had surgery canceled owing to abnor-

mal laboratory tests: two owing to anemia, two to an abnormal UA, and one because of a prolonged partial thromboplastin time. Both children with anemia were treated with iron and subsequently underwent surgery without complication. Of the abnormal UAs, one was contaminated, and the cancellation of surgery resulted in a complication requiring emergency surgery. The other abnormal UA was a probable asymptomatic bacteriuria, and the infant later underwent surgery uneventfully. These data suggest that a routine UA adds little to the preoperative evaluation of a healthy child, and should be omitted.

(3-6). Those that are clinically important usually can

be predicted from a complete history and physical examination. There have been two previous studies

of preoperative testing of children. However, the

primary focus of one study was on the value of

preoperative chest x-rays (7); the second study was

performed in Puerto Rico, and may have limited

laboratory test results in children requiring elective

surgery to determine the detected abnormalities,

their preoperative medical management if any, and

We have retrospectively evaluated preoperative

Key Words: ANESTHESIA, PEDIATRIC. ANESTHESIA, EVALUATION—preoperative.

applicability to our clinical setting (8).

their effect on perioperative management.

History taking, physical examination, and preoperative testing including a complete blood count (CBC) and urinalysis (UA) are routinely performed before elective surgery in children. An adequate hemoglobin level is necessary for oxygen delivery and serves as a baseline for evaluation of blood loss. Most pediatric anesthesia texts recommend obtaining a preoperative UA, but rarely provide a rationale (1,2). Because the collection of a clean specimen can be difficult and time-consuming in young patients, we questioned whether the use of preoperative UA results in perioperative management confirms the need for this test.

The American Academy of Pediatrics, the American Society of Anesthesiologists, and the American College of Surgeons make no definite recommendations for preoperative testing. Studies of preoperative laboratory testing in adults have shown that most detected abnormalities are clinically unimportant for the scheduled surgery and are ignored by clinicians

After approval from the Committee on Human Research, we reviewed the charts of all patients under 18 yr of age having a nonobstetric elective surgical procedure at San Francisco General Hospital. All charts were reviewed by one investigator. Data collected included patient age and sex, results of the preoperative history, physical examination, CBC and UA tests, the type of surgery and anesthesia, the length of hospital stay, perioperative complications, and previous cancellations of surgery.

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Methods

A CBC included measurements of hemoglobin, hematocrit, red blood cell count (RBC), indices, and total white blood cell count (WBC). Anemia was defined as

- 1. hemoglobin <100 g/L (10 g/dL) in infants 0–3 mo of age;
- 2. hemoglobin <105 g/L (10.5 g/dL) in infants 4-12 mo of age;
- 3. hemoglobin values below the third percentile in children older than 12 mo (9).

Microcytosis was defined as a mean corpuscular volume (MCV) below the third percentile in children older than 12 mo, or <70 fL in children younger than 12 mo (9). A WBC was considered abnormal if it was <3.5 \times 10⁹ (3500/mm³) or >15 \times 10⁹ (15,000/mm³).

Our routine UA consisted of a specific gravity and dipstick readings, including leukocyte/nitrite (LN). The LN tests measure leukocyte esterase and nitrite, which are markers for WBC and bacteria, respectively. A UA with a positive LN, or a UA with $\geq 1+$ on any other dipstick test was considered abnormal, and then a microscopic examination was performed. The UA findings of microscopic hematuria with <5 RBC per high power field; LN+ with <5 WBC per high power field; 1+ proteinuria; and ketones were considered clinically unimportant.

Data were analyzed using a Z statistic with a two-tailed α of 0.05.

Results

Over a period of 36 mo (August 1984 to September 1987), 538 of 1560 pediatric surgical procedures were elective. Of these, 52 were performed using local anesthesia, and 486 using general or spinal anesthesia. The latter 486 patients formed our study group. The male/female ratio was 1.9:1, 317 males and 169 females. Patients were divided into five age groups: <1 yr (n=80); 1–2 yr (n=91); 3–5 yr (n=75); 6–12 yr (n=110); and 13–17 yr (n=130).

The surgical procedures performed are listed in Table 1. Two hundred seventy-three children (56%) were discharged on the day of surgery, 114 (24%) were hospitalized for one night, and 98 (20%) spent more than one night in the hospital. (Data were missing for one child.) Only three children required an intraoperative transfusion. An indwelling urinary catheter was placed intraoperatively in 25 children (5%).

Preoperatively, 85 children (17.5%) had an abnormally low hemoglobin level or a normal hemoglobin

Table 1. Elective Surgical Procedures Performed

Type of surgery	No. of patients, $n = 486 (\%)$
Inguinal herniorrhaphy, hydrocele repair or orchiopexy	107 (22.0)
Myringotomy and tube placement (alone)	47 (9.7)
Excision of soft tissue mass	43 (8.8)
Tonsillectomy and/or adenoidectomy	25 (5.1)
Orthopedic hardware removal	23 (4.7)
Circumcision	21 (4.3)
Mastoidectomy and/or tympanoplasty	20 (4.1)
Nevus removal and/or skin graft	15 (3.0)
Upper urinary tract surgery	12 (2.5)
Intraabdominal surgery	11 (2.2)
Other	162 (33.5)

Table 2. Results of Preoperative Complete Blood Count

	Hemoglobin or MCV	Urinalysis	
Total tests performed	484	453	
Abnormal	85	36a	
Surgery canceled	2	2	
Known abnormalities	12	12	
No follow-up observation	66	12	
Follow-up observation	7	12	
New diagnosis	6	1	
Repeat test normal	1	11	

MCV, mean corpuscular volume.

"Clinically significant abnormalities only. An additional 37 patients had clinically insignificant abnormalities (see text) for a total of 73 abnormal urinalyses.

level with a low MCV (Table 2). Fifty-eight children were anemic, nine with a hemoglobin count of <100 g/L. Five of these nine were 2–3 mo of age; three were 6 mo to 3 yr, and one was 15 yr old. Twenty-seven children had microcytosis alone. An abnormally low hemoglobin level or MCV was a known condition or under treatment in 12 patients and appropriate further testing or treatment was documented in only seven. Three of these seven patients were given iron therapy, three were diagnosed as having thalassemia trait, and one had a second CBC that was normal. Sixty-six of the 85 children with anemia or microcytosis had no documented follow-up observation. The incidence of abnormal hemoglobin or MCV in the five age groups did not differ significantly by age.

Thirteen children (2.7%) had an abnormal WBC: 11 with values $>15 \times 10^9$ and two with values $<3.5 \times 10^9$. One elevated WBC was thought to be secondary to a chronic otitis media. The remaining 12 were unexplained, with no documented follow-up. None of these children had surgery canceled.

Results of UA were available for 453 of 486 pediatric patients and 73 results of UA (15%) were abnormal (Table 2). Thirty-six of these abnormalities were

<u>Table 3</u>. Indications for Surgical Cancellations (n = 70)

Indication	Number (%)	
Nonmedical	22 (31.4)	
Abnormal labs only	5 (7.1)	
Anemia	2 (2.8)	
Abnormal urinalysis	2 (2.8)	
Other	1 (1.5)	
Abnormal history and physical examination	43 (61.4)	
Upper respiratory infection	23 (32.9)	
Otitis media	6 (8.6)	
Wheezing	3 (4.3)	
Viral infections	3 (4.3)	
Skin lesions	3 (4.3)	
Further diagnostic workup needed	3 (4.3)	
Fever	1 (1.4)	
Possible pregnancy	1 (1.4)	

judged clinically important. There were no cases of occult glycosuria. Of the clinically significant abnormalities, 12 were related to a known condition, under evaluation, or considered secondary to menstruation. Follow-up study in another 12 revealed normal repeat UAs or urine cultures in 11 (including two attempts at bladder catheterization), and contraceptive counseling for a 13-yr-old girl who had sperm in her UA. The remaining 12 had no documented follow-up. Toddlers aged 1–2 yr were significantly less likely to have an abnormal UA.

Surgery was canceled 70 times (Table 3). Forty-eight cancellations were due to medical reasons, 43 of which were attributed to abnormalities detected during history taking and physical examination, and only five (1% of all surgical patients) were due solely to abnormal laboratory results. Cancellation was significantly more likely in infants <1 yr of age, and less likely in adolescents.

Laboratory-detected abnormalities causing cancellation included anemia (n=2), abnormal UA results (n=2), and an abnormal partial thromboplastin time (PTT) result (n=1). One anemic child was a 21-moold healthy female with a hemoglobin of 94 g/L. Iron deficiency was diagnosed and her hemoglobin level increased with iron therapy. She underwent surgery uneventfully 1 mo later. The second anemic child was a 2-mo-old male (born at 34 wk of gestation) whose preoperative hemoglobin level was 80 g/L. Time and iron therapy raised his hemoglobin level to 105 g/L, and he had surgery 2 mo later without complication.

The two infants having abnormal UA results were both 3 mo old. One, an uncircumcised, afebrile, healthy-appearing male, had the following UA results from a specimen collected by bag: LN+ with 20–50 WBC, 0–2 RBC, and trace bacteria. His WBC was 20.5×10^9 . Suprapubic aspiration was not attempted because he had extremely large bilateral

inguinal hernias. When the penile foreskin could not be retracted for bladder catheterization, a second specimen was collected by bag and sent for culture. He was treated with antibiotics for a possible urinary tract infection. The urine culture grew >100,000 colonies of multiple organisms that were believed to be contaminants. One week later, before surgery could be rescheduled, he presented with an incarcerated inguinal hernia requiring emergency surgery.

Results of UA from the 3-mo-old, afebrile, healthy female showed LN+, trace blood, 5–10 WBC, and 1+ bacteria on a specimen collected by bag. A suprapubic aspiration urine sample grew >100,000 colonies of *Escherichia coli*. The infant was treated for a urinary tract infection although she remained clinically healthy. Surgery was performed 2 mo later without complication.

The 7-yr-old boy who had a mildly prolonged PTT had a detailed hematologic evaluation that revealed no obvious cause for the prolonged PTT. The child underwent tonsillectomy and adenoidectomy without complications 5 mo later, despite a persistently prolonged PTT.

Discussion

Before the late 1970s, a chest x-ray was a routine preoperative requirement before elective surgery in children. When studies by Wood and Hoekelman (7), Brill et al. (10), and Farnsworth et al. (11) showed that the preoperative chest x-ray revealed few clinically important abnormalities that were not suggested by history and physical examination, the American Academy of Pediatrics recommended eliminating this requirement (12). This change has reduced radiation exposure in children and produced savings in time and money.

The desire to decrease costs of medical care, while not compromising quality of care, has been a major force behind recent studies evaluating preoperative testing in adults. Delahunt and Turnbull (3) studied 860 adults undergoing elective surgery and found 172 abnormal test results, 63 of which were not predictable by history and physical examination. However, none of these results altered patients' perioperative management. In a study of 2000 adults, Kaplan et al. (4) found that 60% of routinely ordered tests would not have been performed if test selection had been based on history and physical examination. In their study only 0.22% of unindicated tests revealed abnormalities that might have affected perioperative management. Muskett and McGreevy (5) found that 477 of 1271 (35.3%) preoperative tests performed on 200 adult patients showed abnormal results, but only 76 (5.9%) changed patient management. Of these 76 abnormalities, only five were not predictable, and these were minor. No operations were canceled solely because of preoperative test results.

There are two previous studies of preoperative testing in children. Rossello et al. (8) studied 690 children in Puerto Rico undergoing elective surgery. Only five (0.7%) had a hematocrit below 30%; only one of the five had surgery delayed, and that was due to coexisting illness. One hundred twenty children (17.2%) had a WBC either <4.5 \times 10 9 /L or >11 \times 10⁹/L. Only nine of these children had surgery canceled and all of them were ill. Abnormal UAs were found in 52 of 688 children. Only two had surgery canceled. One child had a coexisting illness and the second a documented urinary tract infection. Wood and Hoekelman (7) examined preoperative hematocrit values in 1918 children. Thirteen children (0.7%) had values <30%. Twelve underwent surgery without complication, eight of whom had no documented follow-up study; one child had surgery canceled. Preoperative UA results were available in 1859 patients: 226 (12.2%) revealed some abnormality, 131 of which were considered clinically important, but only one child had surgery canceled.

Our data are similar to those of Rossello et al. (8) and Wood and Hoekelman (7). Neither of the two infants in our study who had surgery canceled because of an abnormal UA had a definite urinary tract infection. The male infant had a contaminated UA and urine culture, probably owing to colonization of the penile foreskin. The female infant had significant bacteriuria, but was well. Whether this was an early urinary tract infection or an asymptomatic bacteriuria not requiring treatment cannot be determined (13). In our setting, UA results are available before the patient leaves the clinic. This contributes to better follow-up observation of abnormal UA than of abnormal CBC results. More than 80% of the abnormal UAs were either known, considered clinically unimportant, or false-positives. The only new diagnosis made from the UA was a teenager in need of contraceptive counseling. One surgical cancellation due to a probable false-positive UA resulted in patient morbidity. Although our routine screening revealed one child with definite bacteriuria, the effect of asymptomatic bacteriuria on surgery is unknown. We believe that the difficulty in interpretation, the time involved in collection, and the absence of an effect on surgical outcome/management suggest that routine UA testing adds little to the preoperative evaluation of the healthy child.

The incidence of anemia (11.9%) in our patients is

higher than that found in middle-class populations (14) because the population served by San Francisco General Hospital is poor and largely immigrant. Of the seven children with appropriate follow-up of test results indicating anemia or microcytosis, six had new diagnoses established, three of which required treatment. Surgery was canceled in two who had a hemoglobin value <100 g/L. Historically, a hemoglobin of 100 g/L has been the baseline acceptable to most anesthesiologists. This criterion may stem, in part, from a retrospective review of anesthesiarelated cardiac arrests in children (15) which found that 7 of 73 arrests occurred in infants with a hemoglobin value <100 g/L. However, the incidence of anemia in that study population was not reported, and hypovolemia and/or an overdose of anesthetic were apparently present in most cases, complicating interpretation of the data.

A recent National Institutes of Health Consensus Conference convened to assess the relative risk/benefit ratio of perioperative blood transfusions found neither evidence that mild-to-moderate anemia contributes to perioperative morbidity, nor data to support the use of a single criterion for transfusion (16). However, the conference concluded that severe morbidity or mortality could result from the combination of hypovolemia and anemia, and that multiple factors must be considered in deciding whether to transfuse a patient.

Our finding that 74% of children had no follow-up studies or evaluation of abnormal hemoglobin or MCV data is similar to that reported for adults (3–5) and by Wood and Hoekelman (7), and reinforces the perception that the preoperative evaluation is not an effective time for screening. Rare follow-up observation of abnormal test results may be explained by two factors: (a) the CBC and UA results rarely return to the child's primary physician, and (b) most anesthesiologists and surgeons are not concerned about mild degrees of anemia and inconsequential abnormalities of the urine. The high probability of inadequate follow-up study may, however, create medicolegal issues for the physician.

Out data are insufficient to evaluate the preoperative requirement for a hematocrit in pediatric patients scheduled for elective surgery. At San Francisco General Hospital, we have continued our policy of obtaining preoperative hematocrits in all children. Although the collection of the specimen may be painful to the child, the specimen is easy to obtain, the results are readily interpreted, and the false-positive rate is low. Of the patients in our study who had abnormal hemoglobin results that were followed up, more than 40% had a treatable cause for anemia

(iron deficiency). The decision to treat anemia preoperatively is based on multiple factors, including the degree of anemia, the nature and relative urgency of surgery, the anticipated blood loss, the presence of coexisting disease, and the anticipated difficulty with follow-up study. Although the incidence of abnormal CBCs was unrelated to the patient's age, eight of our nine patients with hemoglobin values <100 g/L were <4 yr old. Thus, our policy may be less justified in older children. However, it is necessary to ensure adequate follow-up of abnormal CBC results.

Rossello et al. (8) found that abnormal laboratory test results usually were used to confirm abnormalities found on history and physical examination and rarely used alone to cancel or delay surgery. In contrast, we found that abnormal preoperative test results were rarely used to confirm medical diagnoses. Of 43 cancellations of surgery for medical reasons, 33 were caused by infectious disease. An elevated WBC was detected in only one child (with otitis media) and in one other in whom α -thalassemia trait was diagnosed. Anemia was present in only two cases canceled for noninfectious medical causes. However, we found, as did Rossello et al., that abnormal preoperative laboratory results were rarely the sole reason for cancellation or delay of surgery. Only five of our children (1%) had surgery canceled or delayed solely because of abnormal laboratory studies.

History and physical examination remain the principal sources of information with which to evaluate children for elective surgery. In our setting, we continue to require hemoglobin evaluation in all children scheduled for surgery, but perform a UA only if clinically indicated.

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Effects of Oral Caffeine on Postdural Puncture Headache

A Double-Blind, Placebo-Controlled Trial

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CAMANN WR, MURRAY RS, MUSHLIN PS, LAMBERT DH. Effects of oral caffeine on postdural puncture headache. A double-blind, placebo-controlled trial. Anesth Analg 1990;70:181–4.

Forty postpartum patients with postdural puncture headache (PDPH) were randomly assigned to receive oral caffeine (300 mg) or a placebo. Intensity of headache, quantitated using a visual analogue pain scale (VAS), was assessed immediately before drug administration and 4 and 24 h later. Relief of PDPH measured as ΔVAS (initial VAS – VAS at 4 h) was significantly better in the caffeine than in the placebo group (P=0.014). Six patients (30%) whose PDPH was relieved by caffeine at 4 h had recurrence of symptoms the following day. Our study demonstrates that caffeine administered orally provides relief, albeit if sometimes transient, from PDPH with minimal side effects.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—headache.

Postdural puncture headache (PDPH) is a distressing complication of spinal anesthesia or unintentional dural puncture during attempted epidural anesthesia. Caffeine, a cerebral vasoconstrictor, has long been recognized as able to provide relief to patients with PDPH (1). Only recently has this technique enjoyed a resurgence in popularity. Intravenous caffeine, administered in combination with sodium benzoate (CSB), relieved PDPH in 85% of patients in a double-blind, placebo-controlled study (2). In another study, the combination of intravenous CSB plus hydration provided relief of PDPH in 80% of patients (3). Intravenous CSB appears to be effective in treatment of PDPH. An oral caffeine preparation, although not previously evaluated, would be more convenient and less expensive. Our study evaluated, for the first time, the efficacy of oral caffeine for treatment of PDPH in 40 postpartum patients.

Methods

The protocol was approved by our hospital's Committee for the Protection of Human Subjects from Research Risks. Written informed consent was obtained from all patients. Patients were evaluated within 1-2 days postpartum by either the primary anesthetist or a nurse-clinician, or both. When symptoms were consistent with a PDPH (frontal and/or occipital discomfort worsened by upright posture and relieved by lying supine), one of the investigators was contacted. Upon clinical diagnosis of PDPH, the patient was informed of the study protocol. Patients were excluded from the study if they had preexisting hypertension (or preeclampsia), a seizure disorder, or intolerance to caffeine, or had consumed caffeinated beverages within the previous 4 h. Study participants were requested to consume neither caffeinated beverages nor analgesics during the initial 4-h study interval. No intravenous fluids were administered, and oral intake was ad libitum.

Severity of headache was scored on a 100-mm visual analogue scale (VAS) with 0 = no headache and 100 = worst headache imaginable (4). In a randomized, double-blind fashion, subjects were then given a capsule to consume by mouth. Capsules, prepared by our investigational pharmacy, contained either anhydrous caffeine powder (*USP* 300 mg, Spectrum Chemical Mfg. Corp., Gardena, Calif.)

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Table 1. Patient Characteristics

Characteristic	Caffeine $(n = 20)$	Placebo $(n = 20)$	
Age ^a	29.8 ± 1.4	30.6 ± 1.2	NS
Height (cm) ^a	64.1 ± 0.6	64.6 ± 0.6	NS
Weight (kg) ^a	72.3 ± 2.6	76.5 ± 2.8	NS
Parity			
Primiparous	5	6	NS
Multiparous	15	14	NS
Dural puncture			
26 gauge	14	15	NS
17 gauge	6	5	NS
Delivery			
Vaginal	6	8	NS
Cesarean	14	12	NS
Onset of headache (postpartum)			
Day 1	8	12	NS
Day 2	11	5	NS
Day 3	1	3	NS

NS, not significant.

"Data expressed as mean ± sem.

or placebo (lactose powder) and appeared identical. Headache severity (VAS) was reassessed 4 and 24 h after ingestion of the capsule. When headaches failed to resolve within 4 h, patients were encouraged to rest, to increase fluid consumption, and to take analgesics. Epidural blood patch was explained as a therapeutic option and utilized when those conservative means failed to relieve the headache.

Data were expressed as mean \pm sem. Wilcoxon rank-sum test was used to compare VAS scores between groups. χ^2 analysis was used to compare frequency of blood patch. Student's t-test was used to compare demographic data. P < 0.05 was considered statistically significant.

Results

Forty postpartum patients were studied; 20 received caffeine and 20 placebo. Groups did not differ in age, height, weight, parity, route of delivery (vaginal vs cesarean), size of needle involved in dural puncture (26-gauge spinal vs 17-gauge epidural), or time from dural puncture to onset of headache (Table 1).

Visual analogue scale scores before administration of caffeine or placebo (T_0) did not differ between groups (caffeine 69 ± 3 ; placebo 60 ± 4). Improvement in VAS at 4 h ($T_0 - T_4$) occurred in 18 patients (90%) in the caffeine group vs 12 patients (60%) in the placebo group (Figure 1). At 4 h, VAS scores were lower in the caffeine (33 ± 6) than in the placebo (49 ± 7) group. Moreover, the magnitude of the

decrease in VAS was more than 300% greater in the caffeine than in the placebo group (36 \pm 6 vs 11 \pm 7; P = 0.014) (Figure 2).

At 24 h, 30% of patients in the caffeine group had higher VAS scores than at 4 h. Visual analogue scale scores at 24 h did not differ between the two groups (caffeine 41 ± 8 ; placebo 34 ± 10). Fewer epidural blood patches were required in the caffeine than in the placebo group, but the difference was not statistically significant (35% vs 55%). The patches, when used, always relieved PDPH. There were no significant side effects of caffeine therapy. Two patients in the study complained of mild and transient flushing and jitteriness after receiving their capsule; one of these had received caffeine, the other placebo.

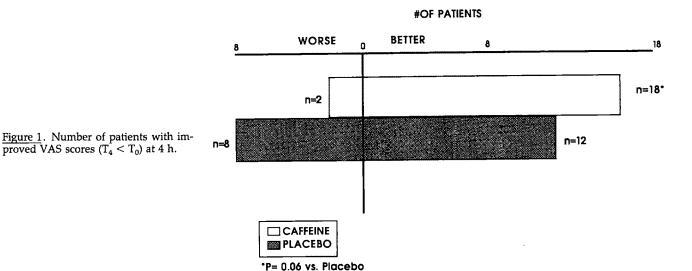
When PDPHs resulting from 17-gauge dural punctures were compared with those resulting from 26-gauge needles, no difference was found in initial pain scores, efficacy of caffeine, or requirement for epidural blood patches.

Discussion

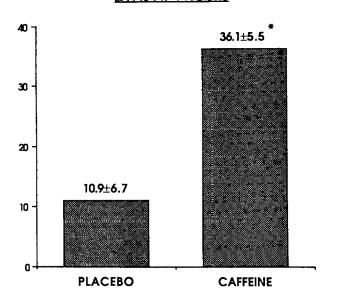
The present double-blind, randomized study demonstrates that a single, oral dose of caffeine (300 mg) provides relief to patients with PDPH. Beneficial effects of caffeine were rapid; relief occurred within 4 h after drug administration, and in 70% of patients, the symptoms did not recur. Side effects were infrequent and mild.

The present findings are in agreement with those from studies using intravenous caffeine. Sechzer and Abel (2) demonstrated salutory effects of intravenous CSB in a randomized study in 41 patients with PDPH. A single 500-mg dose of CSB relieved the headache in 75% of patients, and a second dose, 2 h later, provided relief in an additional 10%. Thirty percent of patients had recurrence of their headache after completion of treatment. Side effects were limited to temporary dizziness and flushing. In a widely quoted, but uncontrolled nonrandomized study, Jarvis et al. (3) reported that PDPH was relieved in 80% of patients treated with intravenous CSB (500 mg) in 1 L of Ringer's lactate solution, followed by an additional liter of Ringer's lactate during the subsequent 2 h. Although the results of the study by Jarvis et al. (3) were promising and consistent with those reported by Sechzer and Abel (2), this nonrandomized study is confounded by the unknown effects of acute 2-L hydration on PDPH, inasmuch as no placebo control was used.

The dose of caffeine used in our study (300 mg of anhydrous powder) was 120% greater than the dose



AVAS AT 4 HOURS



<u>Figure 2</u>. Change in VAS pain score $(T_0 - T_4)$. Values expressed as mean \pm sem. *P = 0.014 vs placebo.

used in the above-mentioned intravenous studies. The CSB dose (500 mg) contains 250 mg of caffeine plus 250 mg of sodium benzoate to enhance solubility before parenteral use (5). As caffeine is almost completely absorbed after oral administration (with minimal first-pass effect) (6), our dosage was similar to that used in the aforementioned studies.

Our study was limited to patients in the immediate postpartum period. During this period caffeine elimination half-life is approximately twice as long as in nonpregnant patients (12–18 h vs 6 h) owing to decreased oxidative metabolism of caffeine (7). Thus, effects of a given dose of caffeine may be more prolonged in the peripartum period than at other

times. The clinical relevance of this pharmacokinetic difference in treatment of PDPH remains to be determined.

An additional concern is whether caffeine ingestion by lactating women exposes the newborn to clinically significant amounts of caffeine. Caffeine is detectable in breast milk after ingestion of either caffeinated beverages (coffee, tea, or cola) (8) or oral tablets (150–300 mg) (9). Amounts of caffeine found were quite small (0.5%–1.0% of maternal dose per liter of milk), and no caffeine was detected in the infant's urine. Only single doses of caffeine were studied and the question of accumulation after multiple doses was not addressed. Thus, although it appears safe to administer a single dose of caffeine to lactating women with PDPH, effects of multiple doses in this patient population are less clear.

Caffeine is available in many beverages and overthe-counter preparations (10,11). However, the caffeine content of a specific beverage (e.g., coffee) may vary widely (Table 2). Thus, a pharmaceutical caffeine preparation, as used in the present study, provides a more exact dosage of caffeine for treatment of PDPH.

The pathogenesis of PDPH is a multistep phenomenon (12). The inciting event is a dural tear and cerebrospinal fluid leakage, which probably leads to intrathecal hypotension. Traction on the meninges and intracranial nerves could produce PDPH. However, a more appealing hypothesis, especially in view of the efficacy of vasoactive drugs on PDPH, is that intrathecal hypotension leads to dilation and distention of intracranial blood vessels (13,14). Indeed, intracranial cerebrospinal fluid pressure that is lower than lumbar cerebrospinal fluid pressure may result in painful dilation of intracranial blood vessels. This

Table 2. Caffeine Content of Common Substances

Substance	Caffeine content (mg)		
Coffee ^a			
Freeze-dried	6 6		
Percolator	107		
Drip grind	142		
Tea ^a			
Black			
1-min brew	28		
5-min brew	47		
Green			
1-min brew	15		
5-min brew	32		
Cocoa ^a	13		
Coca-Cola ^b	65		
Pepsi-Cola	43		
Dr. Pepper	61		
Mountain Dew	55		
Jolt Cola	71		
Chocolate candy bar (1.2 oz)	5		
No Doz ^c (Bristol-Myers)	100		
Vivarin ^c (Beecham)	200		

Data from Bunker and McWilliams (10) except Jolt Cola, from Reference

pressure differential is exaggerated in the upright position, leading to more cerebral vasodilation and worsening pain. Conversely, the pressure differential is decreased or eliminated in the supine position, lessening the stimulus for vasodilation and pain. Thus, PDPH may be explained adequately by alterations in cerebral blood flow (CBF) and spinal fluid dynamics. Caffeine may relieve PDPH because of its ability to increase cerebral vascular resistance, decrease cerebral CBF, and decrease cerebral blood volume (15-17). Recent work by Dodd et al. (18) in support of this theory has indicated the ability of intravenous caffeine to decrease global CBF in patients with PDPH. This decrease in CBF was coincident with relief of headache in all patients (n = 7). Nevertheless, the effects of caffeine on PDPH were transient, in that all seven of Dodd's patients had return of headache 48 h after caffeine, three of whom received epidural blood patches.

In conclusion, this study demonstrates that a single oral dose of caffeine (300 mg) is safe and efficacious, and merits consideration in the early treatment of PDPH. In contrast to intravenous caffeine, therapy with oral caffeine is more convenient and less expensive. Although a majority of patients had relief of headaches without recurrence, some did recur after completion of treatment. The tendency for caffeine, as a single oral dose, to provide only temporary relief

from PDPH precludes its recommendation as a definitive treatment for this syndrome. Whether long-term relief would occur with multiple doses of caffeine in combination with fluids, analgesics, or other vasoactive drugs remains to be determined.

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[&]quot;Coffee, tea, and cocoa measured as 5-oz (150 mL) cup.

^bCola beverages as 12-oz can.

Per tablet.

Should We Inhibit Gastric Acid Secretion Before Cardiac Surgery?

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Stress can decrease intragastric pH and cause erosion of gastric mucosa. Because cardiac surgery and cardiopulmonary bypass represent a major stress, the effects on intragastric pH of an $\rm H_2$ -receptor antagonist, ranitidine, and an $\rm M_1$ -muscarinic antagonist, pirenzepine, were evaluated. Intragastric pH was measured throughout elective cardiac surgery in 60 patients by a digital pH-meter during fentanyl-diazepam-nitrous oxide (50%) anesthesia. The gastric content was sampled at closure of the chest for bacterial count. Oral preoperative medication given randomly included (n = 20 in each group) 0.3 mg/kg diazepam 1 h before induction (group 1); diazepam plus ranitidine (150 mg) 1 h before induction (group 2); and diazepam plus pirenzepine (50 mg) on the evening before surgery and 1 h before induction of anesthesia (group 3).

At induction intragastric pH was higher in group 2 (mean \pm sD = 7.42 \pm 1.07) than in group 1 (5.28 \pm 2.14) (P < 0.01) but was not significantly different in group 3 (5.78 \pm 1.89) than in group 1. In no group did intragastric pH change significantly during surgery. Gastric juice was sterile in 92% of group 1, in 25% of group 2, and in 71% of group 3 patients (P < 0.01). Postoperatively no gastrointestinal complications occurred, but there was a trend toward more patients developing nosocomial pneumonias in groups 2 and 3 (15%) than in group 1 (0%) (P = 0.06). Intraoperative intragastric pH is relatively high after diazepam premedication, thus the preoperative addition of ranitidine or pirenzepine would not be necessary and may possibly be hazardous.

Key Words: ANESTHESIA, CARDIOVASCULAR. GASTROINTESTINAL TRACT, STOMACH—pH, volume.

Cardiac surgery and cardiopulmonary bypass (CPB) cause major stress. Thus they might increase gastric acid secretion and cause stress erosion of the gastric mucosa when intragastric pH (IG pH) is <4 (1). Moreover, acid aspiration syndrome may follow the inhalation of 20–25 mL of gastric juice with pH <2.5 (2). Although acid aspiration syndrome is seen in only 1 of 2131 cases of general anesthesia, it causes death in 4% of these patients (3). The present study was performed to assess these risks in cardiac surgery

and the influence of an H_2 -receptor antagonist, ranitidine, and an anticholinergic agent, pirenzepine, given orally before surgery, on the operative and postoperative course of events.

Methods

The study protocol was approved by the University Ethics Committee. A randomized preoperative treatment was given to 61 adults undergoing elective cardiac surgery with CPB who gave their informed consent. Patients in group 1 only received tablets of diazepam (0.3 mg/kg) 1 h before induction of anesthesia, those in group 2 were given, in addition to diazepam, 150 mg ranitidine, and those in group 3 received diazepam plus 50 mg of the muscarinic antagonist, pirenzepine, both drugs being given at 8 pm on the evening before surgery and again 1 h before induction. The anticipated duration of inhibition of gastric secretion was 8 h (4). Patients with

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previous upper gastrointestinal symptoms, operation, or medications modifying gastric secretion were not included. In particular, patients taking β -adrenoreceptor antagonist medication were not included because β_2 -blockade can increase gastric acid secretion in vagotomized animals (5). All patients stated that they had fasted since midnight on the day before surgery.

Before induction, the degree of sedation was quantitated using a preestablished scale by an anesthetist unaware of the preoperative treatment.

Anesthesia was induced with 30–40 µg/kg fentanyl and 0.1–0.3 mg/kg diazepam followed by 0.1 mg/kg pancuronium; it was maintained with increments of fentanyl and diazepam. The patients were mechanically ventilated with an inspired mixture of 50% nitrous oxide in oxygen. Cardiopulmonary bypass was performed with a bubble oxygenator (Bos 10, Bentley, Plaisir, France) using a nonpulsatile flow pump (Sarns, Ann Arbor, Mich.), total hemodilution, and moderate hypothermia (28°C) with hypothermic cardiac arrest and hyperkalemic cardioplegia. The perfusion index was 2.0–2.4 L·min⁻¹·m⁻²; blood pressure was maintained between 50 and 70 mm Hg using, if necessary, a vasoconstrictor (phenylephrine) or a vasodilator (nicergoline).

Intragastric pH was measured using a digital pH-meter (P 500, Solea-Tacussel, Villeurbanne, France), a glass pH electrode (140 30-3M, Microelectrodes Inc., Londonderry, N.H.) linked to the lower tip of a nasogastric 18 Ch salem sump tube (Sherwood Medical, Petit-Rechain, Belgium), and a cutaneous reference electrode (340 80-1M, Microelectrodes Inc.) applied to the patient's forehead. The pH-meter was calibrated with two standard solutions (pH = 7.00 and 4.65) at operating room temperature, then manually adjusted to 37° C. During hypothermic CPB the pH values were manually adjusted to esophageal temperatures. The measuring range was 0–14 pH and accuracy was ± 0.01 pH within a 6-h period.

Within 5 min of induction a nasogastric tube was passed and its position in the stomach confirmed by auscultation of injected air. Data were recorded immediately after induction, 30 min later, 5 min after starting CPB, every 10 min during CPB, and at closure of the chest. Only data during the first 35 min of CPB were analyzed in order to obtain enough data for statistical significance because a number of CPBs were completed within this time. After measuring intragastric pH, suction of the gastric juice was performed immediately after induction and at closure of the chest with a 50-mL syringe for volume measurement.

At closure of the chest gastric contents were again

sampled but this time were frozen for subsequent bacterial count, under aerobic and anaerobic conditions, on Trypcase soy blood agar. Other culture media included simple or selective media for gramnegative bacteria, *Haemophilus*, *Clostridium*, *Bacteroides*, and fungi. An aliquot of the gastric aspirate (1 mL) was inoculated simultaneously into 25 mL of brain heart infusion broth and kept for 5 days at 35°C. At the end of surgery, the nasogastric tube and the pH electrodes were removed and a single-lumen nasogastric tube was inserted.

Prophylactic cefazolin (25 mg/kg) and netilmicin (2 mg/kg) were administered intravenously at the beginning of surgery and every 8 h thereafter for 48 h.

Postoperative management was at the discretion of a physician unaware of the randomization. Charts were reviewed by one of us, also without knowledge of the randomization. Pneumonia was diagnosed on the basis of x-ray findings, fever, and purulent sputum.

The Kruskall–Wallis test was used to analyze intragastric pH gastric juice volumes and durations. One-way analysis of variance and unpaired Student's t-test were used to analyze other parametric values. Chi-square test with Yates' correction was used for frequency data. Statistical significance was accepted if the P value was <0.05. Most of the results are given as mean \pm sp, including intragastric pH for the reasons stated by Feinstein (6).

Results

Operative Data

Clinical data. Because one patient was excluded from the study, there were 20 patients in each group. Age, sex, ASA physical status, and NYHA classification were not significantly different between groups (Table 1). There were no significant differences in the degree of sedation before induction (Table 2). Despite randomization, weight and CPB duration were significantly different between groups, but there was no significant difference in duration of surgery.

Doses of fentanyl and diazepam standardized for body weight and surgery duration were not significantly different. For fentanyl the figures were as follows: group 1—0.27 \pm 0.09, group 2—0.32 \pm 0.13, and group 3—0.28 \pm 0.10 μ g·kg⁻¹·min⁻¹; for diazepam: group 1—1.98 \pm 0.77, group 2—2.48 \pm 1.46, and group 3—2.14 \pm 0.93 μ g·kg⁻¹·min⁻¹. After CPB sympathomimetic drugs were used 11 times in group 1, 13 times in group 2, and 16 times in group 3. Atropine was used three times in group 2 because of

Table 1. Preoperative Data

	Group 1 $(n = 20)$	Group 2 $(n = 20)$	Group 3 $(n = 20)$
Age (yr) ^a	54 ± 15	55 ± 11	58 ± 11
Sex (M/F)	8/12	13/7	8/12
Weight (kg) ^a	61 ± 9	70 ± 15	58 ± 10
Height (cm) ^a	162 ± 7	165 ± 8	163 ± 10
ASA physical status			
I	3	1	3
II.	6	6	6
III	11	13	11
NYHA classification			
I	2	2	1
II	3	4	4
III	9	8	10
IV	6	6	5

ASA, American Society of Anesthesiologists; NYHA, New York Heart Association.

There were no significant differences between groups except for patients' weight (P < 0.006).

^aMean ± sp.

Table 2. Preoperative and Intraoperative Data

	_	•	
	Group 1	Group 2	Group 3
Psychic state	•		
Agitated	1	0	0
Apparently normal	12	12	6
Euphoric	1	3	4
Drowsy	6	5	10
Operation			
Mitral valve replacement	8	4	6
Aortic valve replacement	5	9	6
Double valve replacement	3	1	7
Triple valve replacement	1	— .	_
CABG	1	. 4	_
Miscellaneous	2	. 2	1
CPB duration (min)"	83 ± 33	69 ± 36	100 ± 47
Surgery duration (min) ^a	220 ± 57	182 ± 81	204 ± 71

CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass. Groups are not significantly different except for duration of cardiopulmonary bypass (group 3 greater than group 2, Kruskall–Wallis test, P < 0.05)

0.05). "Mean ± sp.

excessive bradycardia. Vasodilators were used 9, 16, and 5 times in groups 1, 2, and 3, respectively.

One group 2 patient was excluded from the statistical analysis because he developed fatal uncontrollable hemorrhagic shock during and after CPB. During this period his intragastric pH was >6 as long as mean blood pressure was >40 mm Hg; it then decreased to 1.2.

Intragastric pH. In group 1 (Table 3) postinduction intragastric pH was 5.28 ± 2.14 and intragastric pH did not change significantly during surgery. In group 2 the postinduction value remained significantly higher (7.42 \pm 1.07) than in group 1 (P < 0.01). In

group 3 intragastric pH was not significantly different from that of group 1.

Gastric juice volumes. Immediately after induction and at closure of the chest the gastric volumes were not significantly different between the groups: group 1—median = 2.5 (range 0–45) mL and 30 (0–60) mL; group 2—0.5 (0–50) mL and 11.5 (0–210) mL; group 3—5 (0–25) mL and 40 (0–135) mL, respectively.

Bacteriologic data. Gastric juice was sterile in 92% of group 1, in 25% of group 2, and in 71% of group 3 patients (P < 0.01). When not sterile, the bacterial count yielded 2435 \pm 6215 colony-forming units per milliliter (range 10–20,000 CFU/mL). Streptococcus viridans and coagulase-negative staphylococci, but not anaerobes or fungi, were isolated.

Postoperative Data

Mechanical ventilation lasted 19.0 ± 6.3 h in group 1, 23.2 ± 19.3 h in group 2, and 26.9 ± 15.0 h in group 3 (P > 0.05). Duration of tracheal intubation was 21.6 \pm 6.04, 25.3 \pm 19.3, and 29.6 \pm 15.9 h, respectively (P > 0.05). Patients remained in the postoperative intensive care unit for 2.0 ± 0.7 , 4.3 ± 5.7 , and 3.9 ± 2.3 days, respectively (P > 0.05).

Postoperatively, antacids were administered prophylactically to seven patients and intravenous H₂-receptor antagonists (cimetidine or ranitidine) to eight patients in group 1; in group 2 to ten and eight patients; in group 3 to eight and ten patients, respectively. Two group 3 patients received pirenzepine through the nasogastric tube. There were no gastrointestinal complications except for one group 2 patient who had an episode of epigastric pain on the day after surgery despite cimetidine administered after surgery; this pain was promptly relieved by an oral antacid.

Nosocomial pneumonia developed in no patient in group 1 but in three patients in group 2 and in three patients in group 3. When comparing the number of patients presenting with postoperative pneumonia who were preoperatively treated with ranitidine or pirenzepine versus the other patients, the χ^2 test did not reach statistical significance ($\chi^2 = 3.33$, d.f. = 1, P = 0.06). In five patients the pneumonia was treated with intravenous erythromycin; piperacillin and intratracheal amikacin were given to one patient because the bronchoalveolar lavage yielded gramnegative bacilli. The other patient was treated with vibramycin and methylprednisolone. In all patients, the pneumonia resolved after 11.8 \pm 6.7 days (range 6-24 days) in the intensive care unit.

Table 3. Intragastric pH During Surgery

	A	В	С	D	Е	F	G
Group 1	5.28 ± 2.14	5.06 ± 2.25	5.04 ± 2.02	5.41 ± 2.13	5.62 ± 2.19	5.64 ± 2.18	6.04 ± 1.88
Group 2	7.42 ± 1.07	7.39 ± 1.14	7.26 ± 1.10	7.34 ± 1.54	7.08 ± 2.11	7.01 ± 2.09	7.43 ± 1.19
Group 3	5.78 ± 1.89	5.91 ± 2.08	5.96 ± 1.89	5.97 ± 2.05	5.97 ± 2.08	6.30 ± 1.96	6.62 ± 1.58

Values are mean ± sp.

pH is constantly greater in group 2 than in group 1 (Kruskall–Wallis test, P < 0.01). Group 3 is not significantly different from groups 1 and 2. There is no variation within groups (A: immediately after induction; B: 30 min later; C: 5 min after starting cardiopulmonary bypass; D: 15 min after cardiopulmonary bypass; E: 25 min after cardiopulmonary bypass; F: 35 min after cardiopulmonary bypass; G: at chest closure).

The greatest difference in perioperative intragastric pH between groups occurred 30 min after induction of anesthesia, but there was no significant difference in intragastric pH at this time between patients presenting with or without postoperative pneumonia (pH = 7.18 ± 0.91 vs pH = 5.93 ± 2.13 , P > 0.05). Among the six patients with postoperative pneumonia, three in group 2 and two in group 3 had nonsterile gastric juice. The bacterial count yielded between 40 and 670 CFU/mL.

One patient in group 2 developed sternitis, and one group 3 patient had a urinary tract infection. No infections occurred in group 1. Three patients died of low cardiac output—one in group 2 and two in group 3.

Discussion

Cardiac surgery and CPB are associated with major physiologic stress. During CPB serum levels of stress hormones, particularly catecholamines, increase dramatically (7,8). Because of the vagally mediated gastric acid secretion, a decrease in intragastric pH was expected in the present study. Thus the relatively high intragastric pH found at induction in group 1 (5.28 ± 2.14) seemed surprising. After a placebo premedication Sutherland et al. (9) found intragastric pH to be as low as 2.05; the high intragastric pH value in our group 1 may have resulted from the diazepam premedication. Indeed diazepam has been shown to decrease basal acid secretion in humans (10,11). The high intragastric pH value we observed was essentially unchanged 30 min later, during surgery and after CPB. The high value might also, however, be the result of the fentanyl-diazepam-nitrous oxide anesthesia as Murakami et al. (12) showed in rats that hypothermic stress (core body temperature = 16.9° C) during general anesthesia was associated with higher gastric mucosal blood flow and fewer gastric mucosal lesions than in animals made hypothermic without anesthesia.

After diazepam and ranitidine premedication (group 2) the intragastric pH was significantly higher

 $(7.42 \pm 1.07 \text{ at induction})$ than in group 1, and it remained so throughout the operation. Unlike cimetidine, ranitidine does not seem to retard metabolism of drugs, such as diazepam, that normally undergo high hepatic extraction (13). This is consistent with the similar diazepam dosages administered intraoperatively in all groups. In other studies, with the same preoperative ranitidine dosage similar intragastric pH values were found at induction (9,14). As a gastric pH \geq 4 is deemed to prevent stress erosion of the gastric mucosa (1,15), ranitidine plus diazepam premedication was two times more effective than diazepam alone (90% vs 45% of the patients), whereas values obtained with pirenzepine plus diazepam (60% of the patients) were not significantly different than those obtained with diazepam alone.

Pirenzepine, an M₁-muscarinic antagonist, is thought to interact selectively with cholinergic receptors that mediate gastric secretion (16). When used alone intravenously in intensive care patients, pirenzepine failed to maintain the intragastric pH above 4 (17). In group 3 no significant difference in intragastric pH occurred when compared with group 1, although the pH values in group 3 remained constantly higher than in group 1.

The gastric juice volumes were low both at onset and completion of surgery in all groups. As opioids reduce gastric emptying (18) this suggests that diazepam reduced gastric secretion but that neither ranitidine nor pirenzepine had a significant effect. In two previous studies (19,20) premedication with ranitidine was found to decrease gastric juice volumes, but other studies were unable to confirm this decrease (14,21). The risk of acid aspiration syndrome appears to be low in elective cardiac surgery; furthermore, ranitidine does not entirely eliminate this risk. Thus, prevention of acid aspiration syndrome with ranitidine does not seem routinely necessary before cardiac surgery, although the subject certainly deserves further study. The patient who received ranitidine before surgery and developed hemorrhagic shock had the lowest intragastric pH in this study. Thus it can be recommended that another dose of ranitidine and antacids be given if shock develops during or after surgery.

In mechanically ventilated intensive-care patients, gastric overgrowth of bacteria provides a reservoir for colonization of the esophagus, mouth, and nasopharynx (22,23), probably facilitated by the inability of some patients to swallow and the presence of a nasogastric tube. Prolonged H₂-receptor blockade and associated gastric achlorhydria may weaken the gastric barrier to bacteria and predispose to systemic infection (24). The elevation of intragastric pH caused by antacids or H₂-receptor antagonists favors gastric and pharyngeal bacterial colonization, and, as a cuffed tracheal tube does not provide complete protection (25), these medications may increase the risk of nosocomial pneumonia (26,27) and possibly increase death rates (28). In morbidly obese patients undergoing ring gastroplasty, Laws et al. (29) showed that two preoperative doses of H₂-antagonists increase gastric bacterial growth. Despite a short course of this regimen (between 16 and 20 h) the present study suggests that ranitidine administered orally before cardiac surgery increases bacterial gastric colonization. However, the trend toward higher incidence of infectious complications, especially pneumonias, after ranitidine or pirenzepine treatment must be interpreted cautiously because (a) the number of patients studied was small; (b) the difference between the intragastric pH of patients presenting with or without postoperative pneumonia was not statistically significant; (c) despite randomization the duration of CPB was longer in patients in group 3; and (d) the causes of postoperative pneumonia are multifactorial. On the other hand, obesity, although despite randomization more common in group 2 than in group 1, did not favor the development of postoperative pneumonia because the difference in body weight between groups remained significant after elimination of patients who developed postoperative pneumonia (group 1: 61 ± 9 , group 2: 72 \pm 14, group 3: 60 \pm 8 kg; P < 0.01).

In conclusion, intragastric pH remains relatively high after diazepam premedication and during fent-anyl-diazepam-nitrous oxide anesthesia for cardiac surgery. The preoperative addition of oral ranitidine increases intragastric pH but the muscarinic antagonist pirenzepine has no significant effect. Increasing intragastric pH may protect the gastric mucosa from stress erosion, but it favors bacterial gastric colonization possibly leading to a higher incidence of systemic—especially pulmonary—infections. This complication deserves further study. At present it cannot be recommended that patients having elective cardiac surgery be given gastric secretion inhibitors with premedication.

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Colorimetric End-Tidal Carbon Dioxide Monitoring for Tracheal Intubation

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GOLDBERG JS, RAWLE PR, ZEHNDER JL, SLADEN RN. Colorimetric end-tidal carbon dioxide monitoring for tracheal intubation. Anesth Analg 1990;70:191–4.

We evaluated a colorimetric end-tidal carbon dioxide (ETCO₂) detector (FEF end-tidal carbon dioxide detector, Fenem, New York, N.Y.) during 62 intubations in anesthetized patients who were hemodynamically stable. The intubations were performed during a drill that simulates difficult tracheal intubation and therefore is associated with an increased risk of esophageal intubation. Each intubation attempt was monitored by two anesthesiologists and a research assistant who together used chest auscultation, colorimetric ETCO₂, and capnography to confirm tracheal intubation and detect esophageal intubation. The reliability of the monitors was compared with capnography. Colorimetric ETCO₂ confirmed tracheal intubations and detected esophageal intubations 100% of the time, as judged by capnography. There were no false-positive or false-negative

decisions based on endotracheal tube position; however, one equivocal color change occurred, which was caused by failure to inflate the endotracheal tube cuff. Colorimetric $ETco_2$ monitoring confirmed tracheal intubation more rapidly than did chest auscultation (P < 0.001) or capnography (P < 0.05), and detected esophageal intubation more rapidly than did chest auscultation (P < 0.05) and as rapidly as capnography did. Confirmation of tracheal intubation was achieved earlier than detection of esophageal intubation with all three monitors (P < 0.05). We conclude that colorimetric $ETco_2$ monitoring is a safe, reliable, rapid, simple, and portable method for determining endotracheal tube position for patients who are hemodynamically stable and should be recommended where capnography is not available.

Key Words: INTUBATION, ENDOTRACHEAL. ANESTHESIA, END-TIDAL CARBON DIOXIDE MONITORING—esophageal intubation.

Unrecognized esophageal intubation remains a significant cause of anesthetic morbidity and mortality. In a recent analysis of closed malpractice claims, Cheney et al. (1) found unrecognized esophageal intubation to be the single most critical anesthetic incident associated with catastrophic injury. However, morbidity and mortality from esophageal intubation are not limited to anesthesia. Esophageal intubation occurs with a frequency of 1.8% in comatose patients or patients who have suffered cardiac arrest during out-of-hospital paramedic intubations (2). The incidence of esophageal intubation may be high during cardiopulmonary resuscitation because intubation attempts are performed under less than optimal

conditions caused by ongoing chest compression or incomplete airway equipment, and without the ability to monitor end-tidal carbon dioxide (ETco₂). Furthermore, nontrained and certainly nonexpert medical providers attempt many of these intubations.

The single best detector of esophageal intubation is monitoring of ETco₂ by a capnograph (3). This is because exhaled respiratory gas has a concentration of carbon dioxide (CO₂) 100 times greater than that of air. Capnography relies on infrared or mass spectroscopy to quantitate breath-to-breath CO₂ analysis. In addition to identification of endotracheal tube placement, the capnograph can aid in the diagnosis of various conditions such as air embolism, obstructive lung disease, malignant hyperthermia, rebreathing, and incomplete muscle paralysis. However, a capnograph requires a power source, calibrations, and periodic maintenance, and it is not easily portable. Capnographs are also expensive. Because of this, they are largely confined to areas of high medical technology such as operating rooms and intensive

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care units where the personnel most skilled in intubation practice.

We report the use of a simple colorimetric ETco₂ monitor for the confirmation of tracheal intubation and detection of esophageal intubation in patients during a simulation drill for the unexpected difficult tracheal intubation (4). This drill provides a clinical model for testing the safety and reliability of this device because it is associated with an approximately 25% incidence of recognized esophageal intubation (Goldberg JS et al., unpublished data).

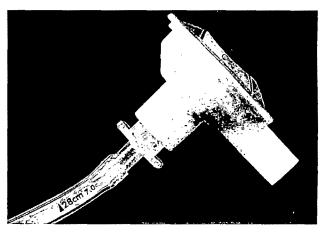
Methods

The study protocol was approved by the Durham Veterans Administration Medical Center Human Studies and Research and Development Committees. Informed written consent was obtained from patients scheduled to undergo general endotracheal anesthesia for noncardiothoracic surgery.

All patients were men aged between 18 and 70 yr; all were classified as ASA physical status I, II, or III. Patients with gastroesophageal reflux or esophageal or tracheal pathology were excluded. Choice of induction technique, including muscle relaxants, was at the discretion of the attending anesthesiologist. Intubation was performed by an anesthesiology resident or a certified registered nurse anesthetist using a simulation drill for the unexpected difficult intubation as previously described by Cormack and Lehane (4). This simulation drill is a method of laryngoscopy that converts a normal glottic view to one in which the glottis is obscured and only the epiglottis is visible. Intubation is performed with the aid of an endotracheal tube introducer, which is slipped under the epiglottis. The endotracheal tube is then slid into position.

Patients were continuously monitored for cardiopulmonary stability using a noninvasive blood pressure monitor (Dinamap, Critikon), pulse oximeter, and five-lead electrocardiogram. Hypoxemia was defined as an arterial oxygen saturation (Sao₂) of <90% by pulse oximetery.

Endotracheal tube position was determined by two anesthesiologists and a trained research assistant who monitored chest auscultation, colorimetric ETco₂ (FEF end-tidal CO₂ detector, Fenem, New York, N.Y.) (Figure 1), and capnography using a B Datex CO₂ Monitor (Puritan Bennett), respectively. The FEF end-tidal CO₂ detector incorporates metacresol purple as an indicator that changes from purple to yellow on exposure to CO₂. A color scale is provided that corresponds to various levels of CO₂ as



<u>Figure 1</u>. Side view of an FEF end-tidal CO_2 colorimeter attached to an endotracheal tube. The open end attaches to the anesthesiabreathing circuit.

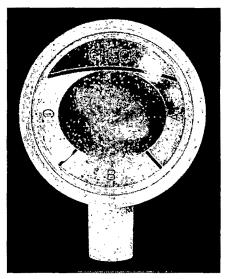


Figure 2. View of the top of an FEF end-tidal CO_2 colorimeter showing indicator in center and color ranges on the perimeter. "Check" is the standard indicator color before use. "A" \leq 2.3 torr CO_2 . "B" is between 3.8 and 7.6 torr CO_2 . "C" \geq 15.2 torr CO_2 .

follows: range "A," purple, \leq 2.3 torr CO₂; range "B," purple-yellow, 3.8–7.6 torr CO₂; range "C," yellow \geq 15.2 torr CO₂ (Figure 2).

The time elapsed from placement of the tube to the decision regarding tube position, a decision based on one monitor assigned to each observer, was recorded with a stopwatch. Each observer was assigned the same monitor throughout the entire study and reached an independent decision as to endotracheal tube placement. Observers were not blinded as to decisions reached by their fellow observers. Confirmation of tracheal intubation was based on auscultation of bilateral breath sounds over the chest, by color change on the colorimetric ETco₂ monitor from purple (range "Check") to yellow (range C), or by the

appearance of a normal waveform on the capnograph. If the attending anesthesiologist determined that an esophageal intubation had occurred as evidenced by the inability to auscultate breath sounds over the chest and absence of a capnogram, the study was discontinued, the endotracheal tube was removed, and the patient was intubated in a standard manner.

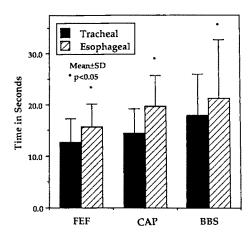
A false-negative result was defined as lack of color change when correct endotracheal tube placement was confirmed by a waveform on the capnograph. A false-positive result was defined as a yellow color change, range C, when esophageal tube placement was detected by an absent waveform on the capnograph.

For statistical analysis, reliability between colorimetric monitoring, capnography, and breath sounds was determined using χ^2 analysis. Analysis of variance was used to determine significant differences in detection and confirmation times between the three methods. Finally, the statistical significance of differences in times for esophageal and tracheal intubations for each method was evaluated using unpaired t-tests.

Results

A total of 62 intubations was performed in 62 patients. There were 51 tracheal and 11 esophageal intubations as defined by capnography. Colorimetric ETco₂, chest auscultation, and capnography all diagnosed endotracheal tube position in all cases ($\chi^2 = 0$, P = 1.0). Colorimetric ETco₂ confirmed tracheal intubation earlier than capnography (P < 0.05) or chest auscultation (P < 0.001). Colorimetric ETco₂ detected esophageal intubation earlier than chest auscultation (P < 0.05), but there was no significant difference between colorimetric ETco2 and capnograph detection times. Colorimetric ETco₂ confirmed tracheal intubation or detected esophageal intubation a mean of 5 s earlier than chest auscultation. With all methods, detection of esophageal intubation required more time than confirmation of tracheal intubation (P < 0.05) (Figure 3).

There were no false-positive or false-negative results with use of the colorimetric $ETco_2$ monitor. There was one equivocal change in the B range (3.8–7.6 torr CO_2) on the colorimetric indicator caused by inadvertent failure to inflate the endotracheal tube cuff when the tube was correctly placed in the trachea. After the cuff was inflated, the color changed to the C range (≥ 15.2 torr CO_2). There was one color change to the A range (≤ 2.3 torr CO_2),



<u>Figure 3</u>. Times for confirmation of tracheal and detection of esophageal intubations using FEF (colorimetric ETco₂ monitoring), CAP (capnography), and BBS (chest auscultation). *Comparison of tracheal intubation vs esophageal intubation by each method. Statistically significant by unpaired *t*-test.

presumably caused by trace respiratory gas contained in the stomach during an esophageal intubation, and this was correctly interpreted as an esophageal intubation.

The esophageal intubations were all followed by successful endotracheal intubations without complications. There was no evidence of hypoxemia in any of the patients.

Discussion

Unlike infrared and mass spectroscopy, colorimetric CO₂ monitors require no electrical power, maintenance, or calibration as they use chemical indicators. In these monitors, a detector is exposed to exhaled respiratory gas. The detector is comprised of a hygroscopic material, a selected colorimetric pH indicator, and a base. The pH of the detector is slightly higher than the transition point, which is the pH at which the indicator changes color. When the detector is exposed to CO₂ in expired respiratory gas, hydrogen ions are formed from the hydration of CO2, the detector becomes more acidic, and the indicator changes color. Desirable aspects of the design of colorimetric monitors include use of stable reagents that do not produce toxic fumes, tubing with low airway resistance, and an indicator that does not change color in the red-green spectrum (as 8% of the population is red-green color blind).

The first colorimetric device for measuring exhaled CO₂ in an anesthesia circuit was designed by W. B. Draper in 1936 in an effort to detect rebreathing (U.S. Patent 2,136,236). He used bromo-cresol purple in calcium carbonate solution to detect increasing con-

centrations of CO₂ in exhaled gas. Berman et al. (5) developed a colorimetric CO₂ indicator using cresol red and phenolphthalein solution with a mucus trap. This apparatus identified endotracheal tube placement but could not be incorporated into the anesthesia circuit because it contained an aqueous indicator. It was not until 1986 that C. G. Fehder (U.S. Patent 4,728,499) developed a colorimetric ETco₂ monitor that provided rapid, nonaqueous, colorimetric detection of esophageal intubation that could easily be incorporated into the anesthesia circuit.

Our results demonstrate that colorimetric ETco₂ monitoring is safe, reliable, and provides early confirmation of tracheal intubation and early detection of esophageal intubation. Colorimetric ETco₂ monitoring confirmed endotracheal tube placement more rapidly than chest auscultation with both esophageal and tracheal intubations. For tracheal intubations, colorimetric ETco₂ monitoring predicted tube placement earlier than capnography, presumably because we were using a sampling or sidestream capnograph, which draws samples of respiratory gas through a long tubing. In addition, colorimetric ETco₂ required only a single breath to detect exhaled respiratory gas because the large CO₂ gradient between exhaled respiratory gas and air favors chemical hydration of CO_2 .

Colorimetric monitoring may be particularly suited for out-of-hospital resuscitation or, indeed, whenever capnographs are not available, because a colorimetric ETco2 device requires no power source and can be carried in one's pocket. When confirmation of endotracheal tube placement is needed during resuscitation, however, colorimetric ETco₂ is faced with the same limitation as capnography. Low cardiac output results in diminished pulmonary blood flow, so that ETco₂ remains in the range of 3.8–15.2 torr CO₂ even when the trachea is successfully intubated (6). This low level of exhaled CO₂ may produce an equivocal color change and that may fail to confirm a successful tracheal intubation. End-tidal CO2 may not increase above 15.2 torr until effective cardiac output is restored. The relative incidence of color change in ranges A, B, and C needs to be defined in this situation. Further investigations are warranted to evaluate this technology in patients with compromised pulmonary blood flow.

Although based on only one instance, our study suggests that slight color change (i.e., to the A range, or <2.3 torr CO_2) is indicative of esophageal intubation and should be interpreted as such. Color change to the B range (3.8–7.6 torr CO_2) during a tracheal intubation is very uncommon in patients with normal cardiovascular status. If it does occur, it should prompt an examination of the endotracheal tube cuff to ensure that it is properly inflated.

Future developments in colorimetric ETco₂ monitoring may include detectors that are sensitive to hypercapnia for monitoring respiratory depression in the intraoperative and postoperative period. This may be especially applicable to patients receiving epidural narcotics or patient-controlled analgesia. Another use of a high-level CO₂ detector would be for the noninvasive determination of ETco₂ in ambulatory patients.

Colorimetric ETco₂ monitoring is safe, reliable, and rapid, and we recommend its use when capnography is not available in patients who are hemodynamically stable.

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Review Article

Normobaric Pulmonary Oxygen Toxicity

Jan Klein, мр

Key Words: OXYGEN, TOXICITY—pulmonary. LUNG, OXYGEN TOXICITY. TOXICITY, OXYGEN.

At the time of the discovery of oxygen (O₂), Joseph Priestley speculated that it might prove of benefit in the treatment of some disease. At the same time he warned that the effects of O₂ might not be uniformly beneficial: "From the greater strength and vivacity of the flame of a candle, in this pure air, it may be conjectured, that it might be peculiarly salutary to the lungs in certain morbid cases, when the common air would not be sufficient to carry off the phlogistic putrid effluvium fast enough. But, perhaps, we may also infer from these experiments, that though pure dephlogisted air might be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body: for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve." (1)

The classic nineteenth-century experiments of Paul Bert and Lorraine Smith proved that O_2 in high concentrations was indeed toxic to healthy mammalian lungs (2,3). Bert demonstrated that it was the increase in partial pressure rather than concentration of O_2 in the inspired atmosphere that was responsible for these deleterious effects. In recent years, a biochemical mechanism involving cellular production of partially reduced metabolites of O_2 has been proposed as a basis for O_2 toxicity. The importance of

enzymatic and other intracellular antioxidant defenses against pulmonary O_2 toxicity is now appreciated. Experimental animal models of increased O_2 tolerance have been extensively investigated, but, as yet, there is no clinically useful means of reducing or preventing O_2 -induced lung injury in humans.

Although this review article presents information on the clinical manifestations, pathology, mechanism, and prevention of pulmonary O2 toxicity, recent developments concerning the mechanisms and prevention of hyperoxic damage in animal models will be emphasized because an increased understanding of these mechanisms may lead to a more rational basis for the clinical use of O₂ and the development of therapeutic measures effective in preventing or decreasing the effects of O₂ toxicity. Data presented here on mechanisms of hyperoxic injury and protection are obtained from experiments done under normobaric conditions and elevated partial pressures of O_2 . The reader is also referred to other reviews (4–9), where certain aspects of the subject may be covered in more detail.

Clinical Manifestations

With exposure to hyperoxia at 1 atm of pressure, the lung is the organ most severely damaged because pulmonary tissue Po₂ is the highest in the body. As pulmonary tissue Po₂ is directly determined by the alveolar Po₂ (10), arterial hypoxemia does not delay the development of pulmonary O₂ toxicity at 1 atm of pressure (11). Exposure to O₂ at a partial pressure in excess of 2 atm of pressure also damages the central nervous system and may result in convulsions (the Paul Bert effect) due to sharply increased brain tissue Po₂ (10). The rate at which O₂ toxicity develops is directly related to the partial pressure of inspired O₂. Until the Apollo fire of 1967 American astronauts breathed 100% O₂ at a pressure of one-third of an

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atmosphere without showing any sign of pulmonary O_2 toxicity. Hence, a high concentration of O_2 may be less damaging at high altitude where the atmospheric pressure is reduced than is the same concentration at normobaric pressure (10).

The precise concentration of O_2 that is toxic to humans has, for obvious reasons, been difficult to establish. Most data regarding the tolerable limits of O_2 breathing have been obtained from normal, healthy, young subjects. Thus, the effects of underlying disease and other factors such as age, nutritional status, endocrinologic status, and the history of previous exposures to oxidants or other substances that may alter protective mechanisms against O_2 toxicity are largely unknown.

The onset of O_2 toxicity may occur after an asymptomatic period, during which no physiologic changes are detectable. In nine young men who breathed 100% O_2 for 6–12 h, no abnormality could be detected in the alveolar-arterial O_2 gradient, pulmonary-artery pressure, total pulmonary resistance, cardiac output, or pulmonary extravascular water volume; in addition, there were no symptoms and no x-ray changes (12).

In conscious subjects, the earliest manifestations of $\rm O_2$ toxicity are symptoms of tracheobroncheal irritation like cough and substernal discomfort. The onset of symptoms of tracheobroncheal irritation, roughly 4–22 h after the start of $\rm O_2$ breathing (13), parallels the occurrence of tracheitis and decreased tracheal clearance of mucus (14). The symptoms of this $\rm O_2$ -induced tracheobronchitis precede changes in pulmonary function tests, but the rate of development of these symptoms is so variable as to be a poor index of $\rm O_2$ tolerance.

The most widely applied index of O_2 toxicity in humans has been the vital capacity (VC), as early respiratory physiologists reported that subjects who breathed 90%-100% O2 for 25-30 h had a decreased VC (13,15). In 1970 it was suggested that decreases in VC could be used to predict the onset, rate of development, and degree of severity of the toxic process in the lung caused by O_2 exposure (16). Subsequently, a mathematical description was developed (17) and named the "unit pulmonary toxicity dose." The unit pulmonary toxicity dose is still used as a guideline for O_2 exposures by the U.S. Navy (18) and others (19,20). Recently, however, the available data set was updated, and a quantitative statistical analysis was performed to evaluate VC as an index of pulmonary O_2 toxicity (21). As previously noted by others (4,22), it showed that a decrease in VC is not really an ideal index of O2 toxicity development. Accurate VC measurement requires a trained subject, is effortdependent, and does not take into account the recovery periods as during intermittent exposure; moreover, the response varies among individuals. As the index is based on the response of an individual of median susceptibility, more susceptible individuals would be at increased risk.

In four healthy subjects, decreases in vital capacity were followed by small decreases in both static compliance and carbon monoxide diffusing capacity after breathing 0.98 atm of O₂ for 48 h (15).

Pulmonary physiologic changes observed and reproduced in normal subjects exposed to O₂ under experimental conditions may be obscured in the clinical setting. For example, patients exposed to 100% O₂ for 21–44 h, compared with a control group exposed to less than 42% O_2 , had no detectable physiologic alterations after cardiac surgery (23). Similarly, there was no evidence of pulmonary O_2 toxicity, judged by respiratory function, in 41 patients having high-frequency jet ventilation of the lungs with at least 80% O₂ for up to 12 days (24). On the other hand, increased ratios of dead space to tidal volume and increased arteriovenous shunting have been reported in patients with irreversible brain damage after ventilation with 100% O_2 for 40 h (25). However, the patients in this study received steroid therapy, which may have affected the outcome.

Although physiologic changes attributable to O_2 breathing include decreases in VC, pulmonary compliance, and diffusing capacity, together with increases in arteriovenous shunting and ratio of dead space to tidal volume, early detection of O_2 toxicity requires more sensitive and specific tests.

Using a bronchoalveolar lavage (BAL) technique in volunteers exposed to more than 95% O₂ for 17 h, a significant alveolar-capillary leak expressed by the presence of increased plasma albumin and transferrin in lavage fluid was detected (26). Similarly, increases of albumin in BAL fluid occurred in a dosedependent manner in subjects inhaling 30%-50% O₂ for a mean of 45 h (27). In the same study, clearance of inhaled technetium-labeled diethylenetriamine pentaacetate, a measure of lung epithelial permeability, was increased in subjects inhaling 50% O₂. Quantitation of hydrocarbons such as pentane or ethane in expired alveolar gas is another development of possible indices of early oxidant damage. Because ethane and pentane are volatile hydrocarbons formed during free-radical-induced lipid peroxidation, the presence of these gases indicates ongoing free radical formation in lung tissue (28). Although in humans pentane production increases within 30–120 min of breathing 100% O₂ (29), a dose relationship between inspired O₂ concentration and ethane or pentane excretion is

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not yet established. In the future, it may be possible to develop a metabolic index for detection of hyper-oxic pulmonary damage. The fact that the lungs' ability to metabolize biogenic amines, polypeptides, and prostaglandins (30–32) decreases soon after hyperoxic exposure might also be used to develop an "early warning" test of O_2 toxicity. To date, use of the tests described above to detect pulmonary O_2 toxicity in the clinical setting in an early phase has been limited for reasons including lack of specificity, problems with reproducibility, and the need for sophisticated equipment.

The above studies, however, do indicate that although early (reversible) physiologic, anatomic, and biochemical changes can be detected after short exposure to hyperoxia using sensitive tests, humans can tolerate 100% O₂ at sea level for 24-48 h without serious pulmonary injury. Pulmonary damage results only with longer periods of exposure in normal subjects (but pulmonary tolerance to hyperoxia may be altered by the underlying disease and other physiologic factors). Inspired O₂ in concentrations of 50%– 100% over longer periods of time carries a risk of lung damage, and the duration of exposure required to produce damage seems to be proportional to the concentration of inspired O_2 . The "safe" level of inspired O2 is not established, but we know that less than 50% O₂ can be tolerated for extended periods of time without serious deleterious effects (4).

Pathology of Pulmonary Oxygen Toxicity

Most studies of pulmonary O₂ toxicity, including ultrastructural morphometry, have been conducted in experimental animals. Few studies have been performed in human subjects; those that have been done have typically been done at autopsy after severe illnesses requiring high concentrations of O_2 (usually delivered by mechanical ventilation). Consequently, although the details and time-course of pulmonary O₂ toxicity are well documented in experimental animals, only the end stages of O_2 toxicity have been studied in humans. However, the sequence of morphologic changes that occurs in the lungs in response to pulmonary O2 toxicity seems to be quite similar in different animal species (4,33–36) and in humans (37), but the duration and relative severity of each phase of the process show species variability.

In most species, exposure to 100% O₂ at 1 atm for 24–72 h is associated with an initial phase of injury during which no significant evidence of morphologic injury is apparent. This phase is characterized by augmentation in the production rates of partially

reduced O_2 species (38) due to increased intracellular metabolism of O_2 (39). These free radicals are associated with alterations in cell metabolism that are not initially associated with changes in lung structure or ultrastructure.

The earliest morphologic changes seen in the inflammatory phase involve subtle changes in endothelial cell structure that result in pericapillary accumulation of fluid (33,37,40). This stage of lung injury is associated with, or rapidly followed by, accumulation of thrombocytes, macrophages, and neutrophils in the lung and the release of soluble mediators of inflammation (40–43).

After exposure of rats to O₂ for 36 h neutrophils are rapidly recruited to the lung (43), and after 48 h the volume of platelets retained in the pulmonary capillary bed almost doubles (41). The appearance of neutrophils in the lung is associated with a rapid increase in the extent of morphologic lung injury (33,40). Neutrophils probably initiate the final stage of lethal pulmonary O₂ toxicity by releasing further mediators of inflammation and, once activated, by producing toxic O₂ species via oxidases on their plasma membranes (7,44). Recently it was suggested that one of these mediators, leukotoxin (9,10-epoxy-12-octadecenoate), plays an important role in the genesis of acute edematous lung damage in pulmonary O_2 toxicity (45). However, the exact role of the neutrophil as a primary mediator of hyperoxic lung injury is under debate. Depletion of neutrophils decreases the toxic effects of hyperoxia (46), but neutropenia induced in rabbits by the administration of nitrogen mustard does not prevent the development of lung microvascular injury and pulmonary edema caused by exposure to hyperoxia (47). Moreover, the presence of preexisting lung damage with accumulation of neutrophils in the lung is generally associated with decreased rather than increased sensitivity to O₂ toxicity. Examples include increased O₂ tolerance in animals after preexposure to sublethal doses of O₂ (33) or pretreatment with Bacille de Calmette et Guétin (BCG) (48), endotoxin (49), oleic acid (50), phosgene (51), or α -naphthylthiourea (52). These observations suggest that the neutrophil may contribute to but is not essential for the development of pulmonary O₂ toxicity.

The contribution of alveolar macrophages to pathologic effects in the lung is not clear. Oxygen in vivo appears to increase the number of macrophages in sections of rat lung but may not increase the number of cells obtainable with standard methods of lung lavage (53). It is suggested that the macrophage is responsible for the influx of neutrophils into the lung by the release of chemotactic factors under

hyperoxia (54). Bacterial clearance in animal lungs in vivo decreases after exposure of animals to 100% O₂ (55). Although bactericidal dysfunction of alveolar macrophages of neonatal rabbits exposed to hyperoxia has been reported (56,57), phagocytotic ability of pulmonary macrophages isolated from adult rats exposed to hyperoxia is normal (58), and the impaired bacterial clearance seen may be due to impaired mucociliary clearance (14). Production of factors such as O₂ radicals and eicosanoids by alveolar macrophages probably contributes to the pathology of lung damage in hyperoxia (59,60), but such an effect has not yet been shown directly.

In the final phase, overt destruction of the capillary endothelium takes place. In rats exposed to lethal hyperoxia approximately 50% of capillary endothelial cells are destroyed in the few hours preceding the death of the animal (33). However, this destruction of endothelial cells does not result in overt lung edema; a pleural effusion, nearly equal in volume to the total lung capacity, and associated plasma volume depletion leading to respiratory or perhaps cardiovascular failure probably constitute the immediate cause of death in O₂-poisoned rats (61–64). Although the mechanism of this effusion deserves further study, the pleural effusion is the hallmark of O₂ toxicity in the rat.

At time of death in rats exposed to a lethal high concentration of O_2 there is no significant change in the number of type 1 or type 2 alveolar epithelial cells, even though some ultrastructural changes occur, including ruffling of the membranes of alveolar type 1 cells and blunting of the microvilli on alveolar type 2 cells. A significant epithelial cell proliferative response or frank epithelial cell destruction has not been documented (33).

In primates, including humans, there appears to be proportionately greater injury to the alveolar epithelium during the destructive phase of O_2 toxicity. In monkeys, the alveolar type 1 epithelium is almost completely destroyed after 4 days in 100% O_2 . Hyperplasia of type 2 alveolar epithelial cells leads to almost total replacement of the alveolar epithelial lining with type 2 cells by the seventh day of exposure (35,40).

With discontinuation of exposure to hyperoxia, or during chronic exposure to sublethal hyperoxia, at least three events may develop as a result of the exposure. The first is the proliferation of type 2 alveolar cells that appears to constitute a restructuring of the alveoli of the lung. The second is a fibroblastic proliferation that may lead to an interstitial fibrosis, one that does not seem to have any utility in recovery and may simply be a manifestation of the

aberrant proliferation of a cell type (the fibroblast) that is relatively insensitive to hyperoxia (33,36). The third event is the development of pulmonary hypertension with major restructuring of the walls of large and small pulmonary arteries. Obliterative and restrictive rather than constrictive changes of the precapillary alveolar unit due to fibrosis and extension of the muscle in the microcirculation appear to be the basis for pulmonary hypertension induced by hyperoxia (65,66).

In Vitro Model Systems

In cell cultures, individual cells exposed to hyperoxia can be damaged without interaction with other cells. This is most extensively demonstrated in endothelial cells. Aortic endothelial cells show evidence of impaired uptake of serotonin after 24 h of exposure to 95% O_2 (67), possibly due to decreased fluidity of the plasma membranes of these cells (68). Although endothelial cells show morphologic changes within 24 h of exposure to 80% O_2 (69), increased albumin permeability of cultured endothelial monolayers becomes detectable only after exposure to 95% O_2 for 3 days (70).

In addition to cell cultures, organ cultures and lung explants have been used to evaluate the effects of O_2 on the lung. Ciliary activity ceases in organ cultures of tracheal epithelium after 2–6 days of exposure to 60%–80% O_2 (71). The exposure of tissue slices of rat lungs to hyperoxia results in a degradation of collagen (72). Damage due to hyperoxia has also been reported in explants of parenchymal tissues from rat and rabbit lung (71,73). Release of chromium 51 indicator from labeled lung tissue in culture showed that significant cell damage occurs within 18 h of exposure to 95% O_2 .

A third in vitro model, the perfused lung, has proven to be a sensitive model for detection of early functional damage to the pulmonary alveolar endothelium. Hyperoxia impairs the ability of pulmonary capillary endothelium in the perfused lung to remove various compounds, including serotonin and prostaglandins, from the pulmonary circulation (30,74, 75).

Mechanisms of Pulmonary Oxygen Toxicity Biochemistry of Oxygen Toxicity

The mechanism of O_2 toxicity at the molecular level is now generally attributed to O_2 free-radical reactions with cellular components. Oxygen free radicals are

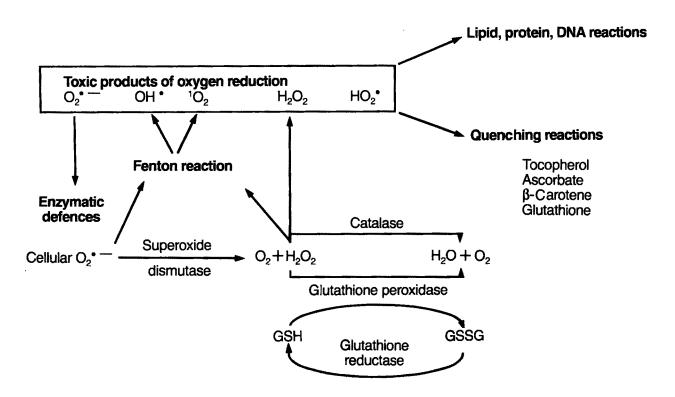


Figure 1. Scheme of free-radical reactions and defense systems.

highly reactive O_2 metabolites that have an unpaired orbital electron. The so-called "free radical theory of O_2 toxicity" attributes the damaging effects of hyperoxia to these highly reactive metabolites of molecular O_2 . These O_2 free radicals are products of normal cellular oxidation-reduction processes. Under conditions of hyperoxia, their production increases markedly. The sources of O_2 free radicals in hyperoxia are unknown but may be the accelerated oxidative processes in pulmonary parenchymal cells and phagocytes (38). The enzyme xanthine oxidase, present in endothelial cells, has also been implicated as a source of toxic O_2 metabolites during hyperoxia (76,77).

The O_2 molecule is normally susceptible to univalent reduction reactions in the cell to form a superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) (39,78). Although it is likely that both the superoxide anion and hydrogen peroxide have direct toxic effects, they interact to produce an even more dangerous species (79). Figure 1 shows the Fenton reaction, which is catalyzed by metals, particularly ferrous iron, and which results in the formation of the harmless hydroxyl ion together with two extremely reactive species, the hydroxyl free radical (OH') and singlet O_2 (1O_2). Although all O_2 radicals are capable of various toxic activities, including lipid peroxidation, depolymerization of mucopolysaccharides, protein sulfhydryl oxidation, cross linking that can lead

to enzyme inactivation, and nucleic acid damage, it seems likely that the hydroxyl free radical and singlet O_2 are mainly responsible for the toxic effects of O_2 (80).

Much evidence has recently appeared concerning endogenous defense systems evolved by organisms to protect their biologic integrity from destruction by free radicals. As O2 free radicals are products of normal cellular oxidative processes, a multilayered biochemical defense system exists that protects organisms against excessive free radical damage (Figure 1). These biochemical defenses, which probably began evolving as soon as the first photosynthetic organisms began discharging O₂ into the atmosphere, an event that can be dated to about 2 billion years ago (81), include both complex enzyme systems and low-molecular-weight free radical scavengers and are a prerequisite for aerobic life. Prototypes of these antioxidant enzymes are the metalloproteins, termed superoxide dismutases (SODs), which neutralize superoxide by conversion to hydrogen peroxide (82). Two enzymes subsequently guard against damage from hydrogen peroxide: catalase and glutathione peroxidase, both of which are capable of degradating intracellular hydrogen peroxide to water; glutathione peroxidase has a more general action and catalyzes the reduction of many hydroperoxides.

The cytoplasmic enzyme glutathione reductase participates in antioxidant defense by reforming reduced glutathione to glutathione. Glutathione, a preferential substrate for many oxidizing agents, is of primary importance in sparing protein sulfhydryl (SH) groups from oxidation.

The low-molecular-weight free radical scavengers include α -tocopherol, ascorbate, and β -carotene, a variety of molecules that preferentially partition into membranes and function by reducing lipophilic free-radical species to less toxic forms. Any molecule that reacts with a free radical can be termed "scavenger"; thus cell components such as sugars, unsaturated amino acids, sulfur-containing amino acids, and unsaturated fatty acids can also scavenge free radicals.

Role of Arachidonic Acid Metabolites

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Arachidonic acid metabolites have biologic properties that can mimic the pulmonary changes produced by hyperoxic exposure. They have potent vasoactive, bronchoactive, and chemoattractant properties, and can increase vascular permeability; all of these are features of hyperoxic lung injury.

Mounting evidence suggests that reactive O_2 metabolites can initiate the release and metabolism of arachidonic acid (60,83–85). Increases in levels of cyclooxygenase as well as lipoxygenase pathway products in BAL fluid have been associated with hyperoxic lung injury (49,86–88), but the administration of a cyclooxygenase inhibitor to block the synthesis of prostaglandins does not result in a decrease but rather an increase in hyperoxic lung injury (49,87). The early increases in prostaglandin levels in BAL fluid that have been documented (49,86,87), therefore, may rather reflect an overall increase in arachidonic acid metabolism, with the increase in lipoxygenase pathway products being at least as important or, perhaps, having a more primary role in mediating the hyperoxic lung injury. Recent reports show reduced mortality, inhibition of neutrophil influx, and a reduction in the increase of BAL leukotriene B₄ levels in a rat hyperoxia model after treatment with the lipoxygenase inhibitor AA861 (89), and attenuation of rat and rabbit lung injury induced by hydrogen peroxide or an oxidant lipid peroxide using various leukotriene antagonists and inhibitors (83,90). A primary etiologic role for lipoxygenase pathway products would provide an explanation for the seemingly contradictory results of studies in which the use of a cyclooxygenase inhibitor resulted in exacerbation of prostaglandin-associated lung injury (87,91). Blockade of just the cyclooxygenase pathway probably results in shunting of arachidonic acid metabolism to the lipoxygenase pathway (92)

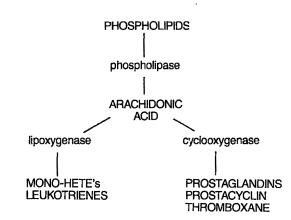


Figure 2. Arachidonate pathway.

(Figure 2). This shunting would result in increased production of lipoxygenase products and, as a consequence, increased lung injury (83,93,94). A complete understanding of this seemingly paradoxical effect of cyclooxygenase inhibitors and the role of lipoxygenase pathway products as mediators of hyperoxic lung injury awaits studies in which measurements of both prostaglandins and leukotrienes in BAL fluid can be performed and the effects of selective inhibitors can be determined.

Role of Pulmonary Surfactant

The change in lung compliance in animals exposed to high concentrations of O_2 suggests involvement of the surfactant system. Although most investigators report that surface activity of the material lining the alveoli is reduced by exposure to O_2 at increased partial pressures (61,95–97), others found normal or increased surface activity, even in the presence of severe pulmonary O_2 intoxication (98).

Increases as well as decreases in surfactantassociated protein synthesis and decreased rates of incorporation of radiolabeled precursors into surfactant phospholipid have been reported (96,99). There are many possible reasons for such inconsistency. One is the large species and age differences in susceptibility to O₂ toxicity; another is the intensity of hyperoxia used and the stage at which animals were studied. Nevertheless, it appears to be reasonably well established that the surface activity of the alveolar lining material is significantly decreased in the lungs of animals exposed to hyperoxia until death from pulmonary O₂ intoxication. Whether the reduction of pulmonary surfactant function occurs as a direct toxic effect of O2 or as a consequence of other adverse effects of pulmonary O2 poisoning (for instance, inactivation of surfactant by intraalveolar

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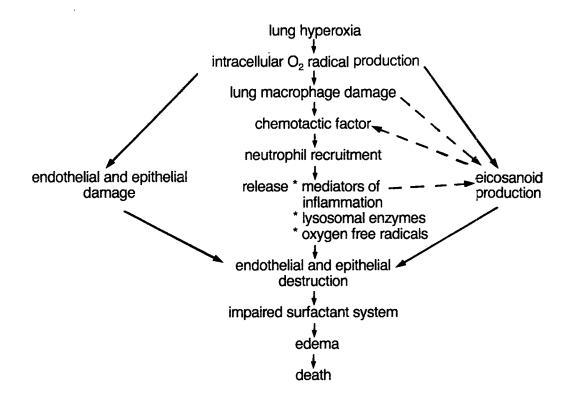


Figure 3. Summary of events leading to hyperoxic death.

edema [100]), remains to be determined. In either case, reduced surfactant function contributes to the pathophysiological changes found during the terminal stages of O_2 intoxication (Figure 3).

Tolerance and Factors Influencing Tolerance to Pulmonary Oxygen Toxicity

Susceptibility of animals to O_2 -induced lung injury varies widely among species (4), which may in part be based on differences in metabolic rate, including the degree of cytochrome P-450 inducibility (101). The response to O2 is also age-dependent: immature animals are less sensitive to O2 toxicity than adult animals (53). The increased threshold of young animals to O₂ toxicity appears to be correlated with their ability to increase concentrations of protective enzymes described above in response to exposure to O₂

Several constitutional and environmental factors may also influence tolerance to hyperoxia. Among factors best explored experimentally are metabolic alterations, diet, administered medications and chemicals, and prior exposure to hyperoxia or hypoxia.

Because hyperoxic damage is dependent on the rate of free-radical production by intracellular metabolic processes, factors that increase cell metabolism—such as epinephrine (103), hyperthermia (104), testosterone (105), and thyroid hormones (106) exacerbate O2 toxicity in experimental animals and may have similar effects in humans. Dexamethasone treatment of rats exposed to hyperoxia also increases O2-induced injury and decreases survival, but this effect seems to be dependent on the time of dexamethasone administration; if given when pulmonary inflammation due to hyperoxia is marked, dexamethasone improves survival and decreases lung damage (107).

Deficiencies of vitamins or trace metals in diets increase the susceptibility of the experimental animal to hyperoxia. The adverse effects of vitamin E and A deficiency in hyperoxic exposure have been especially well documented (52,108,109); while seleniumor copper-deficient diets also lead to increased mortality of rats under hyperoxic conditions (110,111).

Dietary deficiency of protein in rats potentiates toxicity to exposure to hyperoxia due to a lack of sulfur-containing amino acids, which are critical for glutathione synthesis (112). A negative nitrogen balance and deprivation of protein may make patients in the intensive care unit more susceptible to O_2 toxicity. Administration of sulfur-containing amino acids may protect against this possible potentiation of lung injury.

Many compounds used therapeutically are metabolized with the production of free-radical intermediates (these may be O₂-derived) and may worsen O_2 -induced lung injury. A prominent example is the glycoprotein antibiotic bleomycin, which is used clinically in treatment of squamous-cell and germ-cell carcinomas. In animal models, the toxic effects of hyperoxia and bleomycin are synergistic, resulting in more extensive lung injury and fibrosis (113). Exacerbations of recognized or occult pulmonary fibrosis may also occur as a result of the therapeutic use of other antineoplastic agents (including busulfan, methotrexate, cyclophosphamide, and fortified inspired O₂ concentrations) during, for example, anesthesia and in the immediate postoperative period (114,115). The mechanism of bleomycin-induced lung injury involves the formation of a DNA-bleomycin-Fe⁺² complex that has oxidaselike activity, producing a superoxide anion after binding to nuclear DNA (116,117). Disulfiram and nitrofurantoin are similarly metabolized with intermediate production of superoxide or hydroxyl radicals and O₂ expectedly increases its cytotoxicity (44,118). Paraquat, a herbicide that occasionally causes human poisoning, is also more toxic to lungs under hyperoxic conditions (119). Herbicides initiate plant death in a variety of ways, but in many instances they do so by overtaxing or destroying the protective mechanisms that control toxic O_2 species and free radicals (120).

To date there are no studies available on the effects of general anesthesia on pulmonary O_2 toxicity apart from those in which patients have been described who showed an increased susceptibility to O_2 -induced lung injury after the use of fortified O_2 concentrations during general anesthesia due to drug treatment or herbicide intoxication. This could be due to the fact that, generally, anesthesia procedures are too brief to induce pulmonary O_2 toxicity.

The rat is capable of responding to 80%-85% O₂ by increasing concentrations of SOD and the glutathione-related protective enzymes within 3–5 days of exposure (121). Animals preexposed to a sublethal concentration of O₂ are able to tolerate prolonged exposures to 100% O2. Preadaptation of adult rats to hypoxia (10% O₂ for 7 days) also results in tolerance to O₂-induced lung injury and is associated with an increase in SOD concentration (122). On the other hand, preexposure of rats to 40%-60% O₂ does not increase protective-enzyme concentrations and decreases tolerance to subsequent exposure to 100% O₂ (123). These findings suggest that almost lethal levels of superoxide radical production or cell damage are required to increase protective-enzyme concentrations by hyperoxia or hypoxia.

Therapeutic Approaches to Protection from Pulmonary Oxygen Toxicity

Many animal models of increased O₂ tolerance have been investigated, but to date no clinically useful means of reducing O₂-induced lung injury in humans exists. Some experimental models will be discussed here because therapeutic measures effective in preventing or decreasing the effects of O₂ toxicity, based on the results of these animal studies, may be introduced to clinical practice in the near future.

To this point, the most effective pharmacologic agent described for increasing O2 tolerance in rats is bacterial endotoxin. The protection provided by endotoxin is species-specific (rats and lambs develop O₂ tolerance, but mice and hamsters do not; primates have not been tested) (109,124,125). The mechanism of endotoxin protection against hyperoxic injury is not known. This improved tolerance has been associated with increases in lung SOD and other antioxidant enzymes during hyperoxic exposure (42,123, 126). However, the protective effect of endotoxin is blocked by acetylsalicylic acid (91), which interferes with prostaglandin metabolism. Although production of lipoxygenase metabolites by BAL lavage cells is not inhibited by endotoxin (127), inhibition of in vivo free-radical release by lung neutrophils has been proposed as the mechanism by which endotoxin protects rats from O₂ toxicity (128). Endotoxin treatment stimulates the production of at least three potent cytokines: tumor necrosis factor/cachectin, interleukin 1, and interferon. All three factors have been implicated as playing an important role in endotoxin's protective action; pretreatment of rats with either tumor necrosis factor/cachectin and interleukin 1 (129), interferon inducers (130), or simply serum of endotoxin-protected rats (131) decreases lung injury and mortality in hyperoxia. Endotoxin also protects against hyperoxic injury to porcine endothelial cells (132). It has been suggested that endotoxin protects these cultured endothelial cells by prevention of the hyperoxia-induced decrease in plasma membrane fluidity (133). Currently, there is interest in the attempt to modify the endotoxin molecule to produce protective substances that have low inherent toxic action, so-called endotoxoids (134).

Difficulties arise with the therapeutic use of SOD or catalase because they are intracellular enzymes with very short half-lives in plasma. There is, therefore, little scope for their use by direct intravenous injection. However, it is possible for these enzymes to enter cells if they are administered in liposomes, and their plasma half-life may also be extended by conjugation with polyethylene glycol. Experimental

use of SOD and catalase in these forms results in a substantial protection (135–139). Polyethylene glycol conjugation with antioxidants may be more effective than liposome encapsulation (140). Delivery of antioxidants conjugated to polyethylene glycol is improved and their half-lives prolonged compared with liposome encapsulation.

Instillation of exogenous surfactant in rabbits exposed to 100% O₂ for 64 h prevents the development of abnormal lung mechanics and alveolar collapse and mitigates the degree of lung edema, once animals are returned to room air; at least part of this beneficial effect appears to be related to the action of exogenous surfactant in preventing an increase in alveolar surface tension (141).

The leukotriene synthesis blocker AA861 significantly reduces mortality of rats caused by O₂ toxicity when administered intraperitoneally (89). AA861 inhibits leukotriene B₄ production, a chemotactic agent for neutrophils, and thus AA861 would reduce the accumulation of neutrophils in the lung.

Intact erythrocytes placed in the tracheobroncheal tree of hyperoxic rats dramatically improves their chances for survival (142). Lungs from erythrocyte-protected rats show almost none of the morphologic damage suffered by untreated animals. These protective effects of insufflated erythrocytes would be based on their recyclable glutathione. An ironic connotation of these experiments is that small amounts of spontaneous alveolar hemorrhage, a common feature in respiratory distress situations, may actually be beneficial in patients ventilated with O₂ at high inspired tensions.

Continuous infusion of the sulfhydryl compounds cysteamine or *N*-acetylcysteine in rats exposed to 100% O₂ results in a reduced mortality and lung edema caused by hyperoxia (143). As sulfhydryl compounds are among the most important endogenous antioxidant agents, administration of these cellpermeable sulfhydryl compounds probably prevents the oxidation of lung nonprotein sulfhydryls such as glutathione (144).

Desferioxamine is an iron-chelating agent that may prove to have a therapeutic role, as ferrous iron is both a potent source of electrons for conversion to the superoxide anion and a catalyst in the Fenton reaction. In rats, the administration of desferioxamine provides partial protection against hyperoxic lung damage (145).

Pretreatment of rats by inducers of pulmonary cytochrome P-450 results in a marked protection against pulmonary O_2 toxicity. This protection is associated with a substantial increase in the components of the pulmonary cytochrome P-450 system, its

peroxidase activity, and an increased response to hyperoxia by lung antioxidant enzyme activities (146).

Although dietary supplementation of vitamins, proteins, and trace metals provides only partial protection in animals with a deficiency of these factors, dietary supplementation of polyunsaturated fatty acids in newborn rats results in increased lung polyunsaturated fatty acid content and improved hyperoxic survival (147). How lung lipid composition works to influence tolerance to pulmonary O_2 toxicity is not yet known.

Conclusion

The last 25 yr have seen major progress in our understanding of the mechanisms and pathophysiology of pulmonary O_2 toxicity and, in particular, the elucidation of the role of free radicals. Important problems that remain include methods for early detection of hyperoxic damage and the means to augment antioxidant defenses. With the solution of these problems it should be possible to expand significantly the value and indications for the therapeutic use of O_2 .

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Clinical Reports

A Modified Epidural Syringe as an Endotracheal Tube Cuff Pressure-Controlling Device

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Key Words: EQUIPMENT, TUBES—endotracheal cuff pressures.

Intubation of the trachea is associated with many complications, including those resulting from overinflation of endotracheal tube (ETT) cuffs and the resultant increases in ETT cuff pressure. Cuff herniation (1), tracheal edema, tissue erosion (2), tracheal stenosis (3), and tracheal rupture (4) have followed periods of excessive cuff pressure.

Among the recommended techniques for monitoring and modulating ETT cuff pressure are continuous pressure monitoring, venting of pressure via a pressure-regulating (Lanz pressure-regulating valve, NCC Division, Mallinckrodt, Inc., Argyle, N.Y.) or controlling (Pressure Easy cuff pressure controller, Respironics, Inc., Monroeville, Pa.) valve, a water column (5), and time-to-inflation of the pilot balloon after a manual squeeze (6).

Gravenstein and Burwick (7) tested the recoil characteristics of various all-purpose plastic disposable syringes and recommended using the Monoject (Sherwood Medical, St. Louis, Mo.) 6-mL syringe in line with the cuff pilot tube as a means of modulating ETT cuff pressure. We have noticed that the syringes they tested did not consistently vent the pressures to an appropriate level (i.e., <30 cm H_2O), owing to the high resistance of the syringe. We postulated that using a disposable epidural syringe with low resistance and systematically increasing the weight of the piston would produce an inexpensive device that

would reliably and reproducibly vent ETT cuff pressure to the appropriate level.

Methods

A test trachea was created by placing a 7.5-mm-ID Mallinckrodt, Inc. (Hi-Lo) ETT in a 23-mm-diameter glass tube (Figure 1). A Gould, Inc. (Cleveland, Ohio) pressure transducer was attached via a three-way stopcock to the cuff pilot tube. Pressures were measured and recorded using a calibrated Grass Instrument Co. (Quincy, Mass.) polygraph.

We randomly increased cuff pressure with the test syringe to 35–100 mm Hg. With the syringe in-line, the piston was allowed to recoil while held in a vertical position. We tested 10 Monoject 6-mL syringes and 10 Concord/Portex (Keene, N.H.) Pulsator disposable plastic epidural syringes. The appropriate recoil pressure of 15 mm Hg (i.e., 20 cm H₂O) was achieved by adding weights to the piston of the Concord/Portex Pulsator syringe.

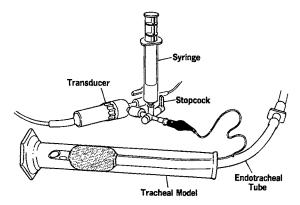
With the appropriate weight added to the piston of the Pulsator syringes, we used the test trachea to test 20 different syringes at three measurements each and to test one modified Pulsator syringe at 50 measurements to determine the reproducibility of results.

With the approval of our Committee of Human Research and written informed consent, we then tested three modified Pulsator syringes in 20 ASA I and II tracheally intubated patients undergoing surgery. After achieving a stable anesthetic state, the anesthetists were asked to estimate the ETT cuff pressure. Cuff pressure was measured using a fluid-filled transducer and a Hewlett Packard Co. (Palo Alto, Calif.) 78342 monitor. With the modified syringe held in a vertical position and positive-pressure ventilation interrupted, we allowed the piston to

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<u>Figure 1</u>. Tracheal model used to measure endotracheal tube cuff pressure before and after recoil of the inflating syringe piston.

recoil until visible movement ceased, then measured postrecoil pressure. We tested the three modified Pulsator syringes, at three measurements each after the anesthetist had overinflated the cuff with variable amounts of air. All pressure venting and measurements were performed by the same investigator (E.R.), who had no knowledge of the volume of air inserted by the anesthetist. Using the same methods, we tested 20 modified Pulsator syringes in a single patient to determine the reproducibility of the results.

Data were analyzed using the unpaired Student's t-test to compare mean pre- and postrecoil pressures in the tracheal model, and paired t-tests to compare mean pre- and postrecoil pressures in the clinical model. Simple regression was used to correlate pre- and postrecoil pressures and anesthetists' mean estimated and measured prerecoil pressures. All pressure results are expressed as mean \pm sd. Statistical significance is accepted at P < 0.05.

Results

Tracheal Model

The mean prerecoil pressure for the 10 Concord/Portex Pulsator syringes was 49 ± 13 mm Hg. Mean postrecoil pressure was 9 ± 1.2 mm Hg (range 7–11 mm Hg). The appropriate recoil pressure of 15 mm Hg was achieved when a total of 10 g was attached to the piston of the Pulsator syringe.

The mean prerecoil pressures of the Monoject 6-mL syringe and the modified Pulsator syringe did not differ significantly (Table 1). However, the mean postrecoil pressure for the Monoject 6-mL syringe was significantly greater and more variable than that observed with the modified Pulsator epidural syringe (46 \pm 10 vs 15 \pm 1.3 mm Hg, Table 1). Pre- and postrecoil pressures were highly correlated for the Monoject 6-mL syringe, but independent of each

<u>Table 1</u>. Tracheal Model: Effect of Recoil of Inflating Syringe Piston on Endotracheal Tube Cuff Pressure

	Pressure		
	Prerecoil (mm Hg)	Postrecoil (mm Hg)	
Monoject 6-mL syringe (n = 49)	54 ± 10 (32–70)	46 ± 10 (22-60)	
Modified Pulsator syringe $(n = 60)$	50 ± 14 (25–70)	15 ± 1.3° (13–19)	

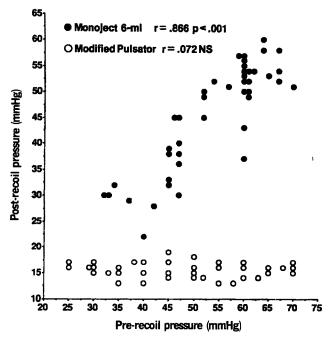
Mean \pm sp (range of values).

other for the modified Pulsator syringe (Figure 2, r = 0.866 vs r = 0.072).

The single modified Pulsator syringe subjected to 50 inflation/deflation cycles had a mean postrecoil pressure of 14 ± 1 mm Hg (range 13-16 mm Hg).

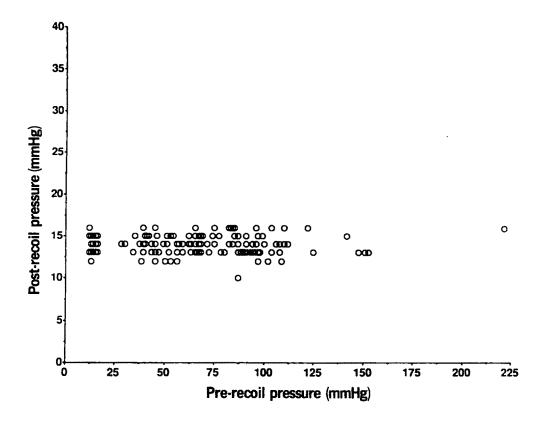
Clinical Model

Figure 3 shows the relationship between pre- and postrecoil pressures for the modified Pulsator syringes in patients. Mean pre- and postrecoil pressures were 75 ± 29 mm Hg (range 28–222 mm Hg) and 14 ± 1 mm Hg (range 10–16 mm Hg) and were independent of each other (Figure 3, r=0.032). The 20 modified Pulsator syringes tested in a single patient



<u>Figure 2</u>. Relationship of pre- and postrecoil of inflating syringe piston on endotracheal tube cuff pressure in the tracheal model. Pre- and postrecoil pressures were directly correlated for the Monoject 6-mL syringe but were independent of each other for the modified Pulsator epidural syringe.

^a P < 0.001 compared with Monoject syringe.



demonstrated mean pre- and postrecoil pressures of 62 ± 31 mm Hg (range 35–150 mm Hg) and 15 ± 1.3 mm Hg, respectively. No air leaks were detected upon the resumption of positive-pressure ventilation after pressure was adjusted with the modified syringes.

Anesthetists consistently underestimated the true ETT cuff pressure. Mean estimated and measured cuff pressures were 35 ± 14 mm Hg (range 20–80 mm Hg) and 74 ± 54 mm Hg (range 6–222 mm Hg). Anesthetists' estimated and true prerecoil pressures correlated poorly (r = 0.34).

Discussion

Tracheal mucosal capillary blood flow begins to decrease when surface pressure exceeds 30 cm $\rm H_2O$, leading to mucosal ischemia and increasing the possibility of mucosal damage and subsequent long-term sequelae (8).

High-volume, low-pressure cuffs were developed to reduce ETT cuff pressure below the level of mucosal capillary perfusion pressure (9). Their advantage over low-volume, high-pressure cuffs is that they occlude and protect against aspiration at pressures of 10–30 cm H₂O. Even with high-volume, low-pressure cuffs, pressures may increase over the recommended limit of 30 cm H₂O because of inadvertent overinfla-

<u>Figure 3</u>. Relationship of pre- and postrecoil of the modified Pulsator epidural syringe piston on endotracheal tube cuff pressure in the clinical model. The pre- and postrecoil pressures were independent of each other. All postrecoil pressures were within a narrow range of 10–16 mm Hg.

tion or the diffusion of nitrous oxide (N_2O) into the ETT cuff (10). Under these circumstances, mucosal ischemia and erosion may occur in the course of a short anesthetic (11).

We have found that the modified Pulsator syringe reliably and reproducibly reduces ETT cuff pressure in both an experimental and clinical model to values falling within the recommended range of 10–30 cm H₂O. In all tests of the Pulsator syringe, pre- and postrecoil pressures were independent. In our tracheal model, the Monoject 6-mL syringe did not perform as well, having unacceptably high postrecoil pressures.

Our findings with the Monoject 6-mL syringe (mean postrecoil pressure 46 ± 10 mm Hg) are not as favorable as compared with those of Gravenstein and Burwick (7), who measured a mean postrecoil pressure of 23 ± 5.5 mm Hg (29.9 cm H₂O) in their lung model. In their study, venting of ETT cuff pressure occurred under conditions of positive-pressure ventilation, which may have forced additional gas out of the cuff with each positive-pressure breath. By venting pressure between positive-pressure breaths or

while positive-pressure ventilation is interrupted, our results are applicable to both spontaneous and positive-pressure ventilation.

The range in the experiment of Gravenstein and Burwick was 14–37 mm Hg (18.2–48.1 cm H₂O), indicating that at least some ETT cuffs would remain at pressures markedly in excess of safe levels when the Monoject syringe was used. In contrast, the modified Pulsator syringes that we tested demonstrated very little variability in performance in either the experimental or clinical models. We believe the lack of variability to be due to the uniformly low resistance and high quality control used in the manufacture of these syringes. The Pulsator syringe costs \$1.50. Two nickels weigh 10 g and fit nicely on the end of the syringe piston.

Our results indicate that estimated cuff pressure by squeezing the pilot balloon is not an effective method of adjusting ETT cuff pressure. The prevalence of overinflated cuffs and the poor correlation between anesthetists' estimates and the true pressure suggest that the problem of excessive ETT cuff pressures is common. A common clinical practice (i.e., just-seal technique) is to adjust ETT cuff volume (and pressure) to eliminate an airway leak at the desired peak inspiratory pressure. Alternatively, the modified Pulsator syringe can substitute for the just-seal technique. When N₂O diffusion into the ETT cuff is expected periodic (e.g., every 30 min) venting of the ETT cuff with the modified Pulsator syringe is recommended (12).

In summary, we have found that a Concord/Portex Pulsator disposable plastic epidural syringe, modified by the addition of a 10-g weight to the piston, can serve as a reliable, reproducible, inexpensive, and readily available pressure-venting device to adjust ETT cuff pressure to a safe range. It performed better than the previously recommended Monoject 6-mL syringe.

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Anesthetic Management of a Parturient With Eisenmenger's Syndrome

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Key Words: ANESTHESIA, OBSTETRIC. HEART, CONGENITAL DEFECTS—Eisenmenger's.

Eisenmenger's syndrome is defined as pulmonary hypertension with bidirectional or right-to-left shunting of blood through an intracardiac or aortopulmonary communication (1). It can occur with complex congenital cardiac malformations, septal defects, and patent ductus arteriosus (PDA). Patients with Eisenmenger's syndrome are at high risk for peripartum morbidity and mortality (2–4). We report the intrapartum use of upper and lower extremity pulse oximetry and administration of spinal morphine in a parturient with Eisenmenger's syndrome secondary to a PDA.

Case Report

A 23-yr-old white woman, gravida 2, para 0, spontaneous abortion 1, was referred to the University of Iowa Hospitals and Clinics for perinatal care. She had a history of dyspnea on exertion and episodes of cyanosis in early childhood. At 6 yr of age, cardiac catheterization showed a PDA with equalization of pulmonary and systemic pressures. The lesion was considered inoperable because of severe pulmonary hypertension.

She was at 27-wk gestation when referred. One week earlier she had experienced a transient cerebral ischemic attack characterized by left-sided sensory and motor deficits. Physical examination revealed obvious cyanosis and clubbing. Her weight was 44 kg and her height was 160 cm. Blood pressure was 150/90 mm Hg and heart rate was 80 beats/min. Lungs were clear. There were grade II/VI systolic and

diastolic murmurs and a right ventricular lift. Ultrasound examination showed oligohydramnios and a growth-retarded fetus (<2.5th percentile for estimated head and abdominal circumferences) in a frank breech presentation, without obvious congenital anomalies. Estimated fetal weight was 437 g. Maternal hemoglobin concentration was 15.0 g/dL and hematocrit was 44%. Blood chemistry and coagulation studies were within normal limits. Arterial blood gas analysis, obtained from the right radial artery while the patient was breathing room air, showed pH 7.42, Po₂ 74 mm Hg, and Pco₂ 28 mm Hg. Pulmonary function tests showed mild obstructive and restrictive changes and decreased diffusing capacity. Echocardiogram was consistent with severe right atrial and right ventricular enlargement, pulmonary hypertension, pulmonic regurgitation, and a PDA.

The patient was admitted to the hospital for strict bed rest and administration of supplemental oxygen. Initially she was managed expectantly, but she rapidly developed signs and symptoms of preeclampsia. The obstetricians decided to effect delivery for maternal indications. Because of the low estimated fetal weight and the morbidity associated with surgery, vaginal delivery was elected. Maternal monitors used during labor and delivery included an electrocardiogram, left radial arterial and right internal jugular central venous pressure catheters, an apnea monitor, and pulse oximeter probes on the right hand and left foot.

While breathing room air, arterial oxygen saturation (Sao₂) was 94% in the right hand and 84% in the left foot. Supplemental oxygen (8 L/min by face mask) increased the Sao₂ to 100% and 89% in the right hand and left foot, respectively. The similar increases in hand and foot Sao₂ with administration of supplemental oxygen suggested that the amount of right-to-left shunt did not change significantly in response to supplemental oxygen.

Just before induction of labor, lumbar puncture was performed at the L4-5 interspace with a 26-gauge needle, and 1.5 mg of morphine was injected into the

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subarachnoid space. Initial hemodynamic measurements, obtained while the patient was receiving 8 L/min of supplemental oxygen via face mask, included an arterial blood pressure of 118/53 mm Hg, heart rate of 53 beats/min, respiratory rate of 28 breaths/min, central venous pressure (CVP) of 5 mm Hg, and Sao₂ of 100% (right hand) and 89% (foot). A 500-mL IV infusion of normal saline over 20 min increased the arterial pressure to 140/64 mm Hg and CVP to 11 mm Hg; Sao₂ remained 100% in the right hand and increased to 95% in the foot. Low-dose heparin, 45 U/h IV infusion, was begun because of the history of a transient ischemic attack and the high risk of a peripartum thromboembolic event. Labor was induced with intravaginal prostaglandin E2 gel followed by intravenous oxytocin. Throughout the first stage of labor external fetal heart rate monitoring showed a rate of 120-140 beats/min with decreased long-term variability, but without deceleration.

The patient had excellent analgesia throughout the 14-h first stage of labor. During this time arterial pressures remained stable. However, as CVP decreased to <8 mm Hg, Sao₂ decreased in the foot. Therefore, intravenous fluids were administered to maintain the CVP at 8–12 mm Hg.

When the patient first experienced perineal discomfort, the obstetrician administered a pudendal nerve block with 1% lidocaine. The patient was uncomfortable during administration of the block, and the Sao₂ decreased to 77% in the foot, but remained at 100% in the right hand. Two 25- μ g IV boluses of fentanyl were given. With the onset of perineal anesthesia, the Sao₂ in the foot increased to 90%. Assisted breech delivery resulted in the birth of a 445-g female infant. Apgar scores were 0 at 1 min and 2 at 5 min. Umbilical arterial blood pH was 6.74. The infant was intubated and ventilated in the delivery room and then taken to the neonatal intensive care unit. On the fifth day of life the infant died of prematurity, respiratory distress syndrome, and sepsis.

After delivery the patient was transferred to the cardiovascular intensive care unit. Phenytoin therapy was begun for seizure prophylaxis. The physician who directed the postpartum management of this patient believed that insertion of a pulmonary artery catheter would provide useful information. Therefore, a pulmonary artery catheter was placed under fluoroscopic guidance, but it was never possible to obtain a pulmonary capillary wedge pressure. Pulmonary arterial pressure always equaled systemic arterial pressure. Data obtained from measurement of cardiac output and calculation of systemic and pul-

monary vascular resistances did not affect patient management.

One day postpartum the heparin was discontinued because of upper gastrointestinal bleeding. Two days postpartum the patient became progressively hypoxemic. A ventilation-perfusion scan showed large bilateral defects consistent with pulmonary emboli. Heparin was restarted, and coumadin was begun. On the fifth postpartum day, the patient left the hospital against medical advice. One month postpartum the patient died suddenly while on the psychiatric service at another hospital. The presumed cause of death was a thromboembolic event. A postmortem examination was not performed.

Discussion

Several authors have recently suggested that it is safe to administer epidural anesthesia to patients with Eisenmenger's syndrome (4–7). However, in each of these reports it appeared that the patients' pulmonary vasculature dilated in response to oxygen. In Eisenmenger's syndrome the amount of right-to-left shunt depends in part on the ratio of systemic vascular resistance (SVR) to pulmonary vascular resistance (PVR). Epidural anesthesia causes a sympathetic block that reduces SVR. If SVR decreases without a concomitant decrease in PVR, the amount of right-to-left shunt increases. Others have observed that both acute and chronic administration of oxygen may decrease PVR in some patients with congenital heart disease (8,9), primary pulmonary hypertension (10), and chronic bronchitis (11). Therefore, the administration of oxygen may reduce right-to-left shunt by decreasing PVR; but this occurs only if the pulmonary vasculature dilates in response to oxygen. Alternatively, administration of an α -adrenergic agonist agent may increase SVR more than PVR and thus reduce right-to-left shunt. In our patient, there were similar increases in oxygen saturation of the right hand and the foot in response to increased inspired oxygen concentration (Fio.). Therefore, we presumed that supplemental oxygen did not dilate the pulmonary vasculature and decrease the right-to-left shunt. Also, we wished to avoid the administration of α adrenergic agonists because of their potential to cause uterine artery vasoconstriction and decreased uterine blood flow (12,13). Consequently, we considered it undesirable to induce a sympathetic blockade that might have resulted in an increased right-to-left shunt as we had no satisfactory method of avoiding or treating an increased right-to-left shunt.

Epidural opioid administration was considered for analgesia during the first stage of labor. However, the

obstetric plan was to begin heparin therapy at the beginning of labor. Owens et al. (14) reviewed the literature and found no evidence of increased risk of epidural hematoma after spinal or epidural anesthesia in the presence of low-dose heparin. However, others have considered systemic anticoagulation a contraindication to placement of an indwelling catheter in the epidural space (15–17). Spinal (i.e., subarachnoid) morphine provides satisfactory analgesia during the first stage of labor (18-20). In our patient, a single injection of spinal morphine was given before the first dose of heparin and an indwelling catheter was not required. We elected to give a large dose of morphine to insure the provision of profound analgesia throughout the first stage of labor. We acknowledge that high-dose spinal opioid administration is associated with a risk of respiratory depression (21-23). However, the patient had continuous nursing care and was monitored with a pulse oximeter and an apnea monitor to allow prompt detection of respiratory depression. A pudendal nerve block provided anesthesia for the second stage of labor. This block provides perineal anesthesia, but avoids the cardiovascular effects of spinal or epidural anesthesia. The effect of pain on the patient's shunt fraction was observed just before administration of the pudendal nerve block. The Sao₂ remained at 100% in the hand but decreased to 77% in the foot; we presume that the lower extremity desaturation was caused by increased right-to-left shunt. Analgesia, provided by systemic fentanyl and the pudendal nerve block, quickly increased the Sao₂ to 90% in the foot. This change suggested a decreased right-to-left shunt.

There is controversy as to whether a pulmonary artery catheter is necessary for monitoring parturients with Eisenmenger's syndrome. Gleicher et al. (3) stated that all parturients with Eisenmenger's syndrome should be monitored with a pulmonary artery catheter. Devitt et al. (24) stated that a pulmonary artery catheter is indicated for patients with Eisenmenger's syndrome secondary to interatrial or aortopulmonary communications but not interventricular communications. They contended that measurement of right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure allows determination of the pressure gradient across the site of the shunt, which influences the amount of shunt. (The pulmonary artery catheter cannot be used to measure simultaneous right and left ventricular pressures and therefore is not useful in predicting shunt fraction in cases of ventricular septal defect.) But Robinson (25) argued that in all patients with Eisenmenger's syndrome, the risks of pulmonary artery catheter-related complications (e.g., pulmonary artery rupture, arrhythmia, thrombosis, embolus) outweigh the potential benefits.

We had several concerns about placing a pulmonary artery catheter in our patient. First, we were concerned about the possibility of arrhythmia with a subsequent decrease in cardiac output and pulmonary blood flow. Second, we thought it possible that thrombus could form around the foreign body and embolize into either the lungs or paradoxically into the systemic circulation. Third, we were aware of the increased risk of catheter-induced pulmonary artery rupture in the presence of pulmonary hypertension (26). Fourth, we were concerned about the possibility of PDA occlusion by the inflated balloon tip with subsequent failure of the right side of the heart. Fifth, we thought that the hemodynamic data measured with a pulmonary artery catheter might not be valid or might be misleading if used for calculation of cardiovascular function. (For example, changes in cardiac output measurements might have reflected a true change in cardiac output, a change in shunt fraction, or a change in both.) Finally, this patient had equalization of pulmonary and systemic arterial pressures as determined by cardiac catheterization when she was 6 yr old. Therefore we expected pulmonary artery pressures to equal systemic arterial pressures. This expectation was confirmed in the postpartum period.

Although we chose not to monitor pulmonary artery pressure, we thought it necessary to monitor CVP. This patient had pulmonary hypertension, right atrial and ventricular enlargement, and right ventricular hypertrophy. The high PVR placed the right ventricle at risk for failure. The left ventricle, however, ejected against a normal vascular resistance and thus was not at risk for failure. Right ventricular failure is best detected by right atrial pressure measurements, whereas left ventricular failure is detected by measurement of either left atrial or pulmonary capillary wedge pressure. Therefore, we elected to monitor CVP and not pulmonary artery pressure.

We used simultaneous pulse eximetry of the right hand and foot as a monitor of both pulmonary function and shunt fraction. Blood flow to the right arm is predominantly preductal; thus Sao₂ in the right arm is determined primarily by FI_{O2}, pulmonary function, and cardiac output. Blood flow in the lower extremities is postductal; therefore Sao₂ in the lower extremities is dependent not only on FI_{O2}, pulmonary function, and cardiac output, but also on the degree and direction of shunt through the PDA. When the Sao₂ of the right arm is constant, the Sao₂ of the foot changes inversely with the amount of right-to-left shunting through the PDA. With an FI_{O2} of 0.21 the

saturation in the right hand was 94%. With supplemental oxygen (8 L/min by face mask) the Sao₂ of the hand increased to 100%. Whereas the Sao₂ of the hand remained at 100%, the Sao₂ of the foot varied between 75% and 95%. We interpreted decreased foot Sao₂ as representing increased right-to-left shunt. Shunt increased with CVP less than 8 mm Hg and with pain. By providing optimal preload (CVP between 8 and 12 mm Hg) and adequate analgesia, we were able to minimize the amount of right-to-left shunt.

In summary, we have presented the peripartum anesthetic and obstetric management of a patient with Eisenmenger's syndrome secondary to a PDA. High-dose spinal morphine provided adequate analgesia for the first stage of labor, and a pudendal nerve block provided anesthesia for the second stage. Monitoring systemic arterial pressure, CVP, and upper and lower extremity oxygen saturation allowed continuous estimation of changes in intravascular volume, peripheral perfusion, and shunt fraction. Postpartum placement of a pulmonary artery catheter did not provide any additional useful information in this patient.

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Nonpigmenting Fixed Drug Eruption After Anesthesia

Henri Desmeules, MD, FRCPC

Key Words: ALLERGY, CUTANEOUS—thiopental. SKIN, ALLERGY—thiopental. ANESTHETICS, INTRAVENOUS—thiopental.

Allergic drug reactions during general anesthesia are either systemic or cutaneous. The former can be life-threatening whereas the latter are frequently self-limited and benign, consisting usually of a transient rash. Recently, we encountered a patient who had a peculiar and rare type of cutaneous reaction, a fixed drug eruption, after general anesthesia.

The term fixed drug eruption was first used by Brocq in 1894 to describe a specific type of reaction to phenazone (1). Since then, many drugs have been associated with this reaction (2,3). The lesions are distinctive; they appear within 24 h of the administration of the offending drug and consist of large, symmetrical, well-demarcated, and painful erythematous plaques. The lesions may be associated with macules or vesicules. These plaques reappear in exactly the same sites every time the responsible drug is administered. The patient usually complains of a burning sensation, and the lesions fade without leaving any trace of pigment after 2-3 wk. The most common locations are the palms, soles, glans penis, lips, and groin areas. Another form of the reaction is called pigmenting fixed drug eruption. In this type of reaction hyperpigmented patches remain at the site of the lesions for months to years. The pathogenesis of fixed drug eruptions has not been fully elucidated (4). A serum factor may be implicated (5). Nonpigmenting fixed drug eruption is not related to porphyria or porphyria cutanea tarda.

Report of a Case

A 66-yr-old woman underwent general anesthesia for corneal repair after a keratoplasty performed 2 mo

earlier. She was given no premedications. During the anesthesia IV drugs included thiopental, succinylcholine, and atracurium. Nitrous oxide and isoflurane were the only drugs given by inhalation. The anesthesia was uneventful. Approximately 24 h after the anesthesia, the patient noted the appearance of large, erythematous, well-circumscribed plaques symmetrically located in her axillae, groins, pubis, flanks, and intergluteal fold. They were accompanied by an annoying burning sensation.

The Department of Anesthesia was informed of the events 48 h after the general anesthesia. On physical examination the patient complained of tenderness and burning sensation at the site of lesions. She was afebrile. The importance of the lesions was striking (Figures 1 and 2). Questioning the patient revealed that the same reaction occurred after her last four or five anesthetics but the anesthesiologists were not informed of these facts. On one occasion, 3 yr previously, the patient had no reaction after general anesthesia. At that time anesthesia was induced with methohexital sodium instead of thiopental. This was the only difference in the drugs used during the anesthesia and suggested a link between thiopental and appearance of the lesions.

During the last admission the patient was referred to the dermatologic clinic for further investigations, and the diagnosis of nonpigmenting fixed drug eruption was confirmed. She was treated with topical steroids and an antihistamine. The reaction disappeared without sequelae within the next 15 days. Subsequently the patient was tested for sensitivity to d-tubocurarine, atracurium, succinylcholine, and pancuronium. These tests were negative. The patient was not tested for sensitivity to thiopental because these tests give conflicting or negative results in fixed drug eruption (5). Administration of a challenge dose was rejected because of the discomfort that it might cause to the patient. Furthermore, the history and the exclusion tests all pointed toward thiopental as the causative agent.

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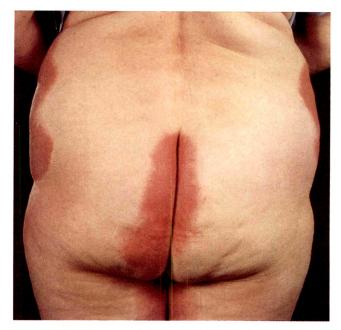


<u>Figure 1</u>. Front view of the patient. The extent and symmetry of the lesions can be fully appreciated.

Discussion

Fixed drug eruption has been rarely reported after general anesthesia. In 1982, Butler et al. reported one such reaction after the administration of thiopental (6). We can presume that this reaction is more frequent than it is actually reported because it develops several hours after the anesthesia and that the link between the administration of thiopental and the appearance of the eruption is not generally recognized.

In addition to barbiturates, many drugs can cause a fixed drug eruption. The most common offenders are anovulatory drugs, codeine, meprobamate, morphine, opium, phenacetin, phenolphthaleins, tetracyclines, chlordiazepoxide, acetylsalicylates, pseudoephedrine, sulfonamides, and isoaminile citrate. Before incriminating a drug, the cause should be documented either by elimination or by provocation tests. In the present case the history was clear and eliminated all agents except thiopental. Furthermore, skin test ruled out



<u>Figure 2</u>. Posterior view of the patient showing the importance of the lesion in the intergluteal fold and partial view of the eruption on the flanks. The bilateral involvement can be appreciated.

sensitivity to *d*-tubocurarine, atracurium, succinylcholine, and pancuronium. In some cases the history may not be as clear, and provocation tests may constitute the only means to identify the offending drug. However, a positive test may provoke discomfort for many days. The advantages and inconveniences should be carefully assessed in each case. The most important aspect is to be aware that fixed drug reactions can be associated with anesthesia. If one occurs, the patient should be advised to avoid the administration of the offending drug in the future.

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Causalgic Pain Responding to Epidural but Not to Sympathetic Nerve Blockade

Roger S. Cicala, MD, James W. Jones, MD, and Laura L. Westbrook, MD

Key Words: PAIN, CAUSALGIA. SYMPATHETIC NERVOUS SYSTEM, REFLEX DYSTROPHY—causalgic.

Although the exact pathogenesis of causalgia is unknown, there is evidence that the condition results from an abnormal feedback loop (1). Abnormal afferent input, either peripherally or at the spinal cord level, may cause inappropriate sympathetic nervous system output (2).

Sympathetic nerve blocks have been a mainstay in the diagnosis and treatment of causalgia. We report a case in which sympathetic nerve block was therapeutically ineffective while epidural block was successful.

Report of a Case

A 30-yr-old man sustained a gunshot wound to the right lower quadrant of the abdomen, underwent an exploratory laparotomy with diverting colostomy, and was discharged home after a routine postoperative course. Twenty-nine days after the initial injury the patient came to the emergency room with a 2-day history of burning pain in the right foot. Outpatient treatment was begun with amitriptyline (150 mg/day) and oxycodone. The pain increased, and 7 days later the patient was admitted for evaluation and treatment.

At the time of admission, the patient described a burning pain over the dorsum of the right foot extending medially above the ankle. The affected area was so extremely hyperesthetic that the patient could not tolerate the bedsheets touching his foot. The foot was erythematous and warm, with a skin temperature 3°C warmer than the left. Hyperhidrosis was noted only over the affected area. Range of motion of

the foot and ankle was markedly limited by pain. Radiographs of the sacrum revealed a small sacral fracture at the site of the bullet's impact near the foramen of the second sacral nerve. The patient was afebrile with a normal white blood cell count and erythrocyte sedimentation rate. Electromyography and nerve conduction studies revealed an incomplete lumbosacral plexus injury proximal to the origin of the superior gluteal nerve, and a presumptive diagnosis of causalgia was made.

The patient underwent a right paravertebral lumbar sympathetic block at the levels of L-2 and L-4 using 10 mL of 1% lidocaine at each level. After this procedure the erythema and hyperesthesia resolved, but the burning pain was unchanged. Pain and symptoms returned to their initial severity within 60 min after the procedure. The sympathetic block was repeated the following day with similar results. Further attempts to obtain pain relief included carbamazepine orally, application of a transcutaneous electrical nerve stimulation unit, and a trial of intravenous lidocaine. Physiotherapy to improve range of motion of the affected foot was performed daily, beginning on the second hospital day.

Seven days after admission, the causalgic pain was more severe and the area of hyperesthesia and erythema had spread to include the entire foot and ankle and the medial portion of the leg below the knee. A single caudal epidural injection using 20 mL of 0.5% lidocaine completely relieved all pain and symptoms for 2 h. A continuous lumbar epidural infusion of 0.125% bupivacaine at a rate of 12 mL/h was begun and continued for the next 72 h, during which time the patient remained pain-free and was able to ambulate. Upon termination of this infusion a burning sensation in the right foot returned but spontaneously resolved in 12 h, after which there was complete absence of pain and symptoms. The patient was evaluated 30 and 90 days after discharge. He has required no medications and has had no further pain or symptoms.

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Discussion

Three distinct phases of causalgia have been described by Kleinert et al. (3), including an early vasodilation phase, a later vasoconstrictive phase, and finally an atrophic phase. Several possible mechanisms for the initiation of causalgia (1,4–6) have been proposed, all of which involve abnormal peripheral afferent to sympathetic efferent feedback loops. Classically, sympathetic efferent nerve blockade along with aggressive physical therapy to restore function have been the mainstay of intervention in causalgia. Many other therapies, including intravenous regional techniques using a variety of agents, surgical sympathectomy, and electrical stimulation, have been used successfully (1).

In the present case only incomplete and extremely short-term relief of pain was obtained following lumbar sympathetic blocks. These blocks were performed by an experienced physician and temporarily eliminated the vasomotor and sudomotor changes as well as the hypersensitivity in the affected area, without modifying the burning pain. Certainly the possibility of misdiagnosis of causalgia must be entertained in this case, but we consider the patient's classic presentation of burning pain and hyperesthesia with vasomotor and sudomotor changes after peripheral nerve injury to be diagnostic, even with incomplete resolution after successful sympathetic block.

Complete resolution of all symptoms including pain was finally obtained in this patient after a single caudal epidural block, and long-term relief followed 72 h of continuous epidural blockade with 0.125% bupivacaine. Bupivacaine in this concentration effectively relieves somatic pain and also provides a pharmacologic sympathectomy. As sympathetic block

alone was unsuccessful in relieving all of the patient's symptoms, it may be that interruption of a pathologic afferent to efferent nerve conduction loop was responsible for relieving the patient's causalgia. It is also possible that interruption of the patient's pain cycle was therapeutic by allowing an increased range of motion during physical therapy.

Epidural injection of local anesthetics with corticosteroids (7) or narcotic analgesics (8) has been used successfully to treat reflex sympathetic dystrophies that were incompletely responsive to sympathetic blockade. It appears that epidural infusion of local anesthetics alone may be an effective alternative when sympathetic blocks do not provide relief in patients with causalgia.

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A Life-Threatening Reaction After Propranolol Administration in the Operating Room

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Key Words: ALLERGY, PROPRANOLOL. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—propranolol.

Many drugs used in anesthesia have been associated with allergic drug reactions (1). Several reports document difficulty in treating allergic drug reactions in patients receiving β -adrenergic blockers (2,3). We are unaware of any case reports that have implicated a β -blocker in the precipitation of an anaphylaxislike reaction. We now report, however, a case of lifethreatening cardiovascular collapse associated with propranolol administration 2.5 h after induction of anesthesia.

Case Report

A 68-yr-old man with recurrent biliary stenosis was brought to the operating room for revision of a prior hepatojejunostomy. The patient's general health was good, and he denied having taken any medications before admission. Past medical history was significant for a skin rash presumably secondary to an unknown antibiotic several years before admission. The patient had had general anesthesia and abdominal surgery on several occasions without incident. There was no further history of allergy. The patient had not, to his knowledge, ever received β -adrenergic blocking drugs. The patient was given 1 g cefoxitin intravenously before coming to the operating room and was premedicated with 5 mg midazolam intramuscularly. Anesthesia was induced uneventfully with 5 mg/kg thiamylal and muscle relaxation was achieved with 8 mg pancuronium. The patient's trachea was intubated, and anesthesia was maintained with isoflurane, nitrous oxide, and oxygen. Monitoring included blood pressure by oscillometry, pulse oximetry, electrocardiogram lead II, body temperature, end-tidal CO_2 , urine output, breath sounds by esophageal stethoscope, and neuromuscular blockade by nerve stimulator.

Approximately 90 min after induction (after it was decided that intraoperative cholangiography was not necessary) 6 mg of morphine was given in 1-mg increments intravenously over 30 min for postoperative analgesia. Blood pressure was stable, ranging from 110/60 to 130/80 mm Hg. Approximately 150 min after induction isoflurane was discontinued. While abdominal closure was progressing, anesthesia was maintained with nitrous oxide and oxygen. At this time, the patient's heart rate began to rise from the mid 70s to the mid 80s. He was not believed to be volume depleted, as he had received 3.3 L of lactated Ringer's solution over 2.5 h with minimal blood loss and urine output $>0.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. In an effort to prevent further increases in heart rate during emergence from anesthesia 0.25 mg propranolol was given intravenously. Within 2-3 min of receiving the propranolol the patient developed tachycardia of 130 beats/min and blood pressure fell precipitously to 50/0 mm Hg. Blood pressure failed to respond to 400 μ g of phenylephrine, 10 mg of ephedrine, and 500 mL of lactated Ringer's solution given over several minutes. Three hundred micrograms of epinephrine was given with a return of blood pressure to 140/80 mm Hg and heart rate to 100 beats/min. At this time the abdominal skin was noted to be erythematous with urticaria distributed evenly over the entire abdominal surface. Abdominal closure was completed, and muscle relaxation was reversed before extubation. The patient remained hemodynamically stable in the recovery room, where he received 250 mg hydrocortisone. The erythema, hives, and facial and truncal edema resolved over 1 h and the remainder of the postoperative course was uneventful. Postoperative neurological examination was negative. Postoperative electrocardiograms and serum creatine phosphokinase isoenzyme levels revealed no evidence of myocardial infarction.

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The patient returned to our institution 2 mo after discharge. He was taking no medication at this time. He was skin tested as described by Bousquet (4) ("prick test") using morphine and propranolol. Morphine (10^{-3} mol/L) was used as a positive control. Normal saline was used as a negative control. Propranolol (10^{-5} mol/L) was diluted 10-fold (10^{-6} mol/L) and 100-fold (10^{-7} mol/L) . The patient was sequentially tested with the serial dilutions, beginning with the most dilute solution. The positive-control morphine (10^{-3} mol/L) produced a 4-mm wheal and flare response in the patient; this concentration produced no response in a normal volunteer.

Our patient was advised of his positive response to propranolol and counseled to obtain a MedicAlert (MedicAlert Foundation International, Turlock, Calif.) bracelet documenting sensitivity to propranolol.

Discussion

Adverse responses to drugs administered during anesthesia may be due to dosage errors, known side effects, drug interactions, or drug-induced mediator release. Adverse reactions secondary to drug-induced mediator release from specific cells (mast cells, basophils) may be classified as anaphylactic or anaphylactoid. Anaphylaxis implies immune-mediated immunoglobulin E (IgE) type I hypersensitivity. When unable to prove that IgE was involved or when IgE is not involved, these reactions are conventionally described as representing an anaphylactoid reaction (5). Such reactions are usually unanticipated and often quite severe.

Anaphylaxis is confirmed by demonstrating the presence of specific IgE antibody. This may be done in vitro by exposing serum to RAST (radioallergosorbent) testing, but this test was not possible in the present case as propranolol is not currently available as a RAST. Intradermal skin testing may be used to identify the drug responsible for a reaction that occurred during anesthesia (6), although such testing does not positively identify the mechanism responsible for the reaction (7). A positive skin-test reaction to a concentration of drug that does not produce a wheal and flare reaction in control subjects is highly suggestive that the patient's cutaneous mast cells contain antibodies to the drug. Subsequent administration of that drug to the patient is unwise.

The treatment of severe allergic drug reactions has been recently reviewed in detail (1,8). The mainstays of therapy continue to be the intravenous administration of fluid in large doses, epinephrine, and maintaining airway patency in a hypotensive patient who may have laryngeal edema. α -Agonists such as phenylephrine are theoretically undesirable as they may decrease intracellular concentrations of cyclic adenosine monophosphate in mast cells and basophils and thus stimulate degranulation (1). Epinephrine, on the other hand, increases intracellular cyclic adenosine monophosphate and inhibits degranulation. Norepinephrine may be useful if epinephrine and fluid resuscitation do not restore the blood pressure. Corticosteroids are valuable as prophylaxis in patients with known sensitivity to radiographic contrast media (9), but are of unproven value in the acute treatment of true anaphylactic reactions. H₁antihistamines have not been shown to be efficacious in the early management of these reactions. The larynx should be evaluated before extubation in these patients, as severe laryngeal edema may develop in a small percentage of cases.

In summary, we present a patient who developed a severe life-threatening systemic reaction manifested by hypotension, urticaria, and edema after a small dose of intravenous propranolol. This case emphasizes the fact that severe, life-threatening allergic drug reactions may develop at any time during the course of an anesthetic and may involve drugs not normally associated with these reactions. A quick response by an alert anesthesiologist will decrease the serious morbidity and mortality that may result from these reactions. Skin testing may aid in identifying the offending drug and preventing its future use.

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Letters to the Editor

Postspinal Headache in Older Patients

Key Words: ANESTHETIC TECHNIQUES, SPINAL—headaches.

To the Editor:

There is no generally accepted explanation for the lower incidence of postspinal headache (PSH) in older patients. Vandam and Dripps (1) reported a 10%–16% incidence of PSH in patients aged 10–49 yr and a 2%–4% incidence in those older than 60. The effect of age is an important factor in the clinical practice of many anesthesiologists who may be reluctant to perform spinal anesthesia on young adults (2). Postspinal headache is thought to be due to leak of cerebrospinal fluid (CSF) through the hole created in the dura. This results in lowered intraspinal pressure and consequent traction on intracranial structures, which results in pain when an upright posture is assumed.

Bromage (3) has noted that "the epidural space is not a closed system." Macintosh and Mushin (4) found that fluid will track through the intervertebral foramina and epidural spaces from one side of the spine to the other. However, with age, the tissue around the exits of the foramina fibroses and forms a recognizable structure. This results in a fibrous sheet that blocks off the foramina in the older patients. In these older patients, fluids "injected into the

<u>Figure 1</u>. Epidurograms of older (*left*) and younger (*right*) patients, with permission from Bromage (3).

epidural space are confined within the spinal canal, and they escape less readily along the neurovascular bundles into the paravertebral spaces" (3). In his monograph, Bromage gives an example of epidurograms performed with contrast dyes in younger and older adult subjects that shows lateral spread in the former group but very little lateral spread in the latter group (Figure 1).

We propose that if there is limited egress from the epidural space into which CSF leaks occur, fluid will accumulate and create a pressure column. The increasing pressure in the epidural space will equilibrate with the decreasing spinal subdural pressure and net flow out of the dural hole will cease. This will limit CSF loss and the consequent decrease in intraspinal pressure. This may be the case in the elderly who have a relatively closed epidural space and may be the cause of the lower incidence of PSH in older patients.

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A New Photoradiation Therapy and Anesthesia

Key Words: EYE, RETINOBLASTOMA—photoradiation. ANESTHESIA, OPHTHALMOLOGIC—photoradiation.

To the Editor:

Photoradiation therapy using a hematoporphyrin derivative (HpD), first applied clinically by Dougherty et al. (1) in 1978 in the management of cancers, has since become increasingly used in treatment of retinoblastoma (2). Intravenously administered HpD disseminates throughout the

entire body but soon clears out of normal cells while staying longer in tumor cells. When HpD absorbs light with maximum absorption near 405 nm, a photochemical reaction that releases a singlet oxygen occurs, causing tissue death but sparing the surrounding normal tissue which contains less HpD (3). The major side effect of this therapy is photosensitivity resulting in skin pigmentation and burns. To avoid such side effects, light exposure must be kept minimal during photoradiation, and the patient should be kept in a dark room for about 3 wk until HpD clears out from the body.

Recently, we performed general anesthesia and provided perioperative care for 3 wk on a 3-yr-old girl who underwent photoradiation therapy using argon laser and HpD for retinoblastoma. As the patient was very young, general anesthesia was required to ensure absolute immobility during the therapy. On the fourth day that she was kept in the dark after the intravenous administration of HpD, photoradiation to her eye was done under general anesthesia. She was transferred from the ward to the darkened operating room with her entire body covered in lightproof surgical cloth. Anesthesia was induced and maintained with halothane/N2O/O2 inhalation after attaching a precordial stethoscope, electrocardiogram, and pulse oximeter. Our operation differed from other retinal surgical procedures in the dark, in that all anesthetic management steps, even tracheal intubation and extubation, were performed under dim light in the dark with the assistance of the night vision scope (Noctovision, NEC, Tokyo). Then the patient was kept in a darkened room during the following 3 wk to avoid side effects. During the next 2 mo, the same procedure was performed twice uneventfully.

We monitored the patient with a pulse oximeter, the accuracy of which was not affected by the dye HpD. The emitted light from the oximeter did not injure the skin. When administering anesthesia in the dark, the pulse oximeter was as mandatory as the electrocardiogram and a precordial stethoscope.

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Hyskon (R) (32% Dextran 70), Hysteroscopic Surgery and Pulmonary Edema

Key Words: BLOOD, volume—dextran. SURGERY, GYNECOLOGIC—hysteroscopy with dextran. LUNGS, EDEMA—dextran.

To the Editor:

I read the article by Mangar et al. (1) with great interest.

I agree with the authors that what they have observed was most likely noncardiogenic pulmonary edema precipitated by intravascular absorption of Hyskon (Pharmacia, Piscataway, N.J.). The amount of Hyskon used, as well as the evident dilution of coagulation factors and hematocrit, would be consistent with an increase of intravascular volume to about twice the preoperative level. This would have led to a corresponding increase in the pulmonary capillary wedge pressure and could largely explain the "copious but unmeasured blood loss per vagina" as well as the signs and symptoms of pulmonary edema despite the absence of jugular distention. Pulmonary capillary wedge pressure or at least venous pressure would probably have revealed intravascular volume overload, although, as reported, heart rate and arterial pressure were unchanged.

I disagree, therefore, with the authors' suggestion that this was due to a "direct toxic effect on the pulmonary capillaries." This suggestion was first made by Kaplan and Sabin (2) and subsequently quoted by Zbella et al. (3). Kaplan and Sabin described a patient who developed similar symptoms after receiving 2000 mL of Rheomacrodex (dextran 40) intravenously daily for 4 days to treat a suspected phlebitis. It is not clear whether these authors were aware that dextran 40, as well as dextran 70, are potent plasma expanders primarily indicated for the treatment of severe hypovolemic shock, and that, even in that indication, dosages above 20 mL/kg are not recommended because of the risk of overexpanding the intravascular fluid volume and thereby precipitating pulmonary edema. It stands to reason that essentially normovolemic patients, as those reported by Kaplan and Sabin and by Mangar et al., are even less likely to be able to tolerate excessive expansion of their intravascular volume.

I know of no evidence of a toxic effect of dextran on pulmonary capillaries. No such effects were seen in any of our extensive toxicologic studies in animals. Furthermore, Rutili et al. (4) have shown that even if these capillaries are damaged before the introduction of dextran, the resulting extravascular lung water increase is solely due to an increase in the capillary hydrostatic pressure and similar to that seen after infusion of an equivalent amount of normal saline. The effect is thus a purely physical rather than a chemical one and should therefore respond to purely physical measures to remove the excess intravascular volume, e.g., phlebotomy or, in severe cases complicated by renal failure unresponsive to diuretics, plasmapheresis to

remove the excess dextran, as suggested by Moran and Kapsner (5).

It is desirable to prevent even this purely hydrostatic pulmonary edema, and therefore the surgeon must exercise caution when using Hyskon for uterine distention in extensive hysteroscopic surgical procedures. The systemic absorption of dextran from this solution can, unfortunately, not be predicted accurately for each procedure, but it is directly related to the pressure and amount of Hyskon used and the amount of endometrium traumatized during the procedure. It is important to remember that Hyskon contains more than six times the concentration of dextran used intravenously for the treatment of shock and that therefore even a relatively modest degree of systemic absorption can cause a significant overexpansion of the intravascular volume. Our prescribing information warns about the increased risk for pulmonary edema in surgical procedures with Hyskon lasting more than 45 min, using more than 500 mL of Hyskon, and/or involving large areas of traumatized endometrium. At least the first two of these conditions applied in the case reported.

We are grateful to the authors for bringing these points to the attention of the anesthesiology community.

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In Response:

Thank you for the opportunity to respond to the letter of Dr. Schinagl. Dr. Schinagl disagrees with what he claims is our suggestion that the effects seen were due to a toxic effect on the pulmonary capillaries. What we in fact stated was: "Although the effect may have been due to fluid overload, we feel the evidence favors direct pulmonary toxicity." Clearly, insufficient evidence is available in the clinical setting to make this differential diagnosis. Dr. Schinagl may well be right. On the other hand, Dr. Schinagl provides evidence in his own letter against the fluid-overload hypothesis. To quote him, "The effect is thus a purely physical rather than a chemical one and should therefore respond to purely physical measures to remove the excess intravascular volume, e.g., phlebotomy or, in severe cases complicated by renal failure unresponsive to

diuretics, plasmapheresis to remove the excess dextran, as suggested by Moran and Kapsner."

As stated in our case report, we gave our 46-kg patient 20 mg of furosemide immediately after the onset of pulmonary edema, repeated this dose in 5 min and then, approximately one-half hour later, gave an additional 100 mg of furosemide in the recovery room. We observed no diuresis in response to what should have been a sufficient dose of a potent diuretic. We felt that this nonresponsiveness to furosemide, in a patient who never developed acute renal failure, serves as evidence against fluid overload. An alternative explanation may be that the copious bleeding per vagina, which nearly halved the patient's hematocrit by the time of discharge from the hospital, served as sort of a "natural phlebotomy," removing excess intravascular volume.

We thank Dr. Schinagl for cogently expressing this alternative hypothesis, but wish to point out that either hypothesis remains unproven.

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Back Pain After Epidural Nesacaine-MPF

Key Words: ANESTHETICS, LOCAL—2-chloroprocaine. ANESTHETIC TECHNIQUES, EPIDURAL.

To the Editor:

Fibuch and Opper (1) reported that the incidence of paralumbar muscle pain and spasm was significant after the epidural administration of 2% or 3% chloroprocaine (Nesacaine-MPF). These authors noted intense muscle pain localized to the lower back associated with muscle spasm (1).

I have considerable experience with chloroprocaine in the obstetric, pain clinic, and outpatient settings and have been directly involved in the administration of more than 1100 epidural anesthetics in the past 5 yr, using buffered or unbuffered chloroprocaine. I have noted symptoms similar to those reported by Fibuch and Opper on two occasions after the injection of 2% chloroprocaine through a needle for infiltration of the skin, intracutaneous, subcutaneous, and intramuscular tissues before epidural needle placement. I attributed these symptoms to the acidic pH of the chloroprocaine solution injected into muscle tissue after advancement of the needle to the interspinous ligament. This is in contrast to a study by Morris et al. (2) who

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reported that chloroprocaine injected intradermally or subcutaneously resulted only in moderate pain. However, Morris et al. did not study intramuscular injection. I have not observed any of the symptoms reported by Fibuch and Opper after the use of 2% lidocaine to anesthetize skin and underlying tissues. There is a considerable difference in the pH of lidocaine and chloroprocaine. The pH of 2% chloroprocaine without bisulfite is 4.35 ± 0.13 , whereas that of 2% lidocaine is 6.21 ± 0.02 (measured with an ABL 30 Radiometer Copenhagen blood gas analyzer) (3,4). Local infiltration using needle and syringe injection results in puddling of the injected drug at the site of injection (5). Had Fibuch and Opper used chloroprocaine to anesthetize the skin and underlying tissues, it is conceivable that the pain and muscle spasm observed could have been caused by local irritation of muscle tissue.

It would be of interest to know whether or not Fibuch and Opper used chloroprocaine for local infiltration in any of their patients before epidural needle placement.

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To the Editor:

We found the recent report by Fibuch and Opper (1) very interesting. We have, however, a few comments we would like to make.

First, no mention is made in the article about the type of local anesthetic used for subcutaneous and ligament infiltration before the insertion of the epidural needle. Was Nesacaine-MPF used for this purpose, or was lidocaine given to any or all of these patients?

Second, we find it surprising that none of the patients retrospectively reviewed over a 12-mo period experienced a localized paralumbar pain, as such pain is certainly not a rare event after epidural injection, albeit usually not seen with a frequency of 40%. Perhaps a prospective, randomized trial with different anesthetic agents might be a more appropriate way of evaluating the prevalence of such pain.

Finally, we also find it curious that this pain was not observed in obstetric cases. Lack of early ambulation or greater use of narcotics certainly cannot explain the absence of this type of pain in parturients. Many women receive epidural analgesia for labor and vaginal delivery. They are generally encouraged to ambulate soon after delivery and rarely require narcotic analgesics. Perhaps the absence in obstetrical patients may be related to the differences in muscle tone between the pregnant and nonpregnant states. Connective tissue is influenced during pregnancy by hormones such as estrogen, progesterone, and elastin, which cause it to become softer and more easily stretched (2). This can have a bearing in situations where the muscles may "spasm."

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In Response:

We thank Drs. Schwalbe, Schiffmiller, and Ackerman for their well-taken comments. We apologize for neglecting to mention in our article (1) the local anesthetic and method used for the skin wheal, subcutaneous, and deep-tissue anesthetization before the placement of the epidural needle, as noted by Dr. Schwalbe and Dr. Schiffmiller. Although multiple anesthesiologists were involved in our report, our departmental practice is to use the same local anesthetic for the skin wheal and deep infiltration as is planned for the epidural anesthetic. In all of our patients this was done. Similarly, our standard practice is to use <2 mL of the local anesthetic to anesthetize the skin, subcutaneous tissue, and interspinous ligaments.

In response to the second point of Dr. Schwalbe and Dr. Schiffmiller, we concur that minor pain after epidural injection is not rare. However, we wish to emphasize that the back pain we have observed after the use of Nesacaine-MPF is not a mild localized aching that one would usually see in patients who develop back pain after the insertion of a 17-gauge Tuohy needle. The back pain we have observed was localized to the paralumbar muscle bed and required narcotics and muscle relaxants for relief. This pain resolved 24–36 h postoperatively.

Our inability to document the occurrence of back pain in our obstetric population may in fact be related to the physiologic differences of the pregnant state. One additional point that may be of importance is that most of our obstetrical patients who were given an epidural anesthetic received 3–5 mg of preservative-free morphine in the epidural space after the celivery of the infant. In our patients, the epidural morphine may have masked the back pain sufficiently during the first 24-h period as to make it not clinically observable.

Dr. Ackerman suggests that the subcutaneous infiltration of 2-chloroprocaine before the epidural needle placement might have contributed to the occurrence of back pain, due primarily to the acidic pH of the 2-chloroprocaine solution. It is our opinion that this is a highly unlikely mechanism in our patients, for three reasons. First, we could not document the occurrence of the phenomenon in our patient population using the "old" 2-chloroprocaine preparations. Second, the pain we observed in our patients was not a local irritation near the site of injection, but severe paralumbar muscle pain associated with spasm after the resolution of the epidural anesthesia. Finally, since we discontinued the use of the Nesacaine-MPF preparation in our institution, we have not observed this complication using either the "old" preparation of 2-chloroprocaine or other local anesthetics for epidural anesthesia.

Recently Levy et al. (2) reported on their experience of 54 adult patients undergoing knee arthroscopy using epidural anesthesia. Their study was randomized and doubleblinded, and in it patients were assigned to one of four groups on the basis of the type of anesthesia they received: (a) 3% chloroprocaine without epinephrine (Nesacaine-MPF, Astra); (b) 3% chloroprocaine with fresh epinephrine, 1:200,000 (Nesacaine-MPF, Astra); (c) 2% lidocaine without epinephrine (Astra); and (d) 2% lidocaine with fresh epineprine 1:200,000 (Astra). In all of their patients, the skin and needle tracts were infiltrated with 1-2 mL of 1% lidocaine using a 26-gauge needle. Their results suggested that moderate and severe backaches were significantly more frequent in patients receiving the 2-chloroprocaine preparation (P = 0.018). The addition of epinephrine to the anesthetic seemed to increase the number of backaches. They postulated that low pH and leakage of anesthetic into the paravertebral space may contribute to muscle irritation.

We have postulated that it is not the 2-chloroprocaine per se that is causing the back pain we have observed with the preparation we used. We believe the new formulation of Nesacaine-MPF containing disodium ethylenediaminetetraacetic acid may be the causative factor. In the December 1988 Astra Pharmaceutical Products, Inc., "Dear Dr." letter it was implied that the occurrence of back pain was associated with larger volumes of local anesthetic placed in the epidural space, and it was therefore recommended that anesthesiologists reduce the total volume of 2-chloroprocaine. Reducing the volume of solution placed in the epidural space would also reduce the total amount of disodium ethylenediaminetetraacetic acid, and therefore presumably decrease a potential causative factor. A smaller volume would also, theoretically, reduce the spread of the local anesthetic into the paravertebral space.

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Spinal Somatostatin Studies in Animals

Key Words: HORMONES, SOMATOSTATIN.

To the Editor:

Gaumann et al. (1) report that intrathecal somatostatin at a dose of 0.7 mg/kg in cats and 0.25-2.5 mg/kg in mice produces neurobehavioral and neurotoxic effects, without producing antinociception. I believe two questions must be addressed: First, why was somatostatin administered at a concentration 4-10 times higher (2) and at a dose 70-200 times higher than that employed intrathecally in humans? Second, are animal studies reliable in predicting the analgesic effect of somatostatin? Concerning the first question, it has been found that intrathecal or epidural somatostatin does not produce neurobehavioral or neurotoxic effects in mice, rats, dogs (see Table 1), or monkeys when doses comparable to those administered to humans are used (3-5). Moreover, no toxic effects have been found in the postmortem histopathological examination of the spinal cord of a patient who had received intrathecal somatostatin for treatment of intractable cancer pain over several weeks and whose death was caused by progression of the disease

Whereas in rats bupivacaine given at only one-third of the per kilogram dose necessary for intrathecal anesthesia in humans causes a 30% reduction of the spinal cord blood flow (7), five times the intrathecal somatostatin dose per kilogram that produced analgesia in humans (8) was required to produce a similar effect on the spinal cord blood flow in rats. An 80% reduction in spinal cord blood flow was achieved when the intrathecal somatostatin dose in rats corresponded to 25 times the human intrathecal analgesic dose (9). Furthermore, it comes as no surprise to find that a potent drug administered at a dose several times that of the therapeutic dose might have deleterious effects (10).

The questionable value of animal studies in predicting the analgesic effect of somatostatin in humans is attested to by the difference in responses to spinal injections of somatostatin in humans and in animals. In humans, the epidural administration of 1 mg of somatostatin results in dermatomal distribution of analgesia similar to that seen with the epidural injection of local anesthetics (11). In contrast to local anesthetics, however, the extent of this dermatomal analgesia is independent of the injected volume and can be maintained with low-dose epidural infusion of somatostatin (0.125 mg/h after 0.25 mg initially) despite the fact that only small amounts of epidural somatostatin reach the intrathecal space (12). Moreover, an increase in the dose of epidurally applied somatostatin

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<u>Table 1</u>. Canine Spinal Cord Histopathological Changes After Spinal Injection of Different Doses of Somatostatin or Saline over Various Periods of Time

Type of injection		Dose	Exposure		Dog															
EP	IT	(mg)		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
X		10/h	5	***************************************					***************************************			***************************************						Х		
Χ		10/h	7															^	Х	
X		6/day	672	X	Χ	X	Χ	X	Χ	X	Х	Х	Х						Λ	
	X	10/h	3														Х			
X		NaCl	672											Χ	X	Х	,,			
Χ		NaCl	7													,				X
EP fibrosis		Х		Х				Х	Х	Х	х		Х	Х						
EP in	EP inflammation										,,	, ,		,,	^					
Slig	ght				Χ					Х	Х				Х					
Severe		X																		
Discrete noninflammatory changes			3			Χ	Х	Х					Х							

EP, epidural; IT, intrathecal; EP fibrosis, epidural fibrosis; EP inflammation, epidural inflammation. Neither spinal ganglia nor spinal cord were damaged (3).

(1 mg/h after 0.5 mg initially) produces a total body negative pin-prick response (13). The fact that intrathecal somatostatin is devoid of analgesic effects in cats, rats, and mice (1,4)—unlike what is seen in humans—therefore suggests that the spinal animal models are inadequate for studying the analgesic effects of somatostatin.

There has been no evidence that epidural somatostatin given at doses that produce analgesia in humans causes adverse effects (14-17). Ventilation while breathing room air and during carbon dioxide stimulation is unaffected by epidural somatostatin (11). It is therefore unlikely that epidural somatostatin, in contrast to epidural opiates, carries the risk of respiratory depression. Although an antinociceptive effect of epidural somatostatin in all patients was evident using the pin-prick test (11), in two studies about 40% of patients given epidural somatostatin did not develop complete postoperative analgesia (13,17). Effective doses of epidural somatostatin in the management of postoperative pain remain to be established, as only a small number of patients have received postoperative epidural somatostatin to date and in those the studies were carried out under different experimental conditions (e.g., premedication, anesthetic technique, type of surgery).

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In Response:

There is no question raised by anyone as to the potential toxicity of somatostatin 1-14 in the mammalian spinal cord. This has now been widely demonstrated in systematic studies in three species by several laboratories (mouse, rat,

and cat: References 1–7). The inclusion by Dr. Chrubasik of a supportive table derived from unpublished, non-peer-reviewed data must have been done in jest. There is (a) no histology presented; (b) the volumes of drug administration are not given; (c) the nature of the histologic analysis is unknown; and (d) the manner in which the neuropathologist assessed the slides and whether or not he was blinded is unknown. This report of "no toxicity" in 17 dogs is hardly a useful piece of data and certainly not one that can be cited.

There are two specific issues that are raised by Dr. Chrubasik: animal models and analgesia in humans, and the doses employed.

It is true that the doses of somatostatin 1-14 that we have employed produce little or no antinociception in the animal models we happen to use. This issue does not, however, obscure the basic observation that at the concentrations we have examined, there are significant behavioral and-more important—histopathological indices of damage in animals treated with spinal somatostatin. With regard to the issue of dose, the concentrations that we and others have employed are in fact around an order of magnitude of those that have been reportedly used in humans (see Reference 8 for further discussion). This is significant because it is, we believe, the local concentration that ultimately accounts for the local tissue toxicity. The issue of reporting the drug dose in "mg/kg," as Dr. Chrubasik does in his letter, is irrelevant, unless he believes the drug is having a systemic effect.

As a commentary, we would note that the history of the spinal use of somatostatin in humans is the anecdote of choice in describing how clinical drug investigation should not proceed. We point in contrast to the significant preclinical literature for clonidine. Whether this α -2 agent will find any clinical utility remains ultimately to be seen, but, at the least, the published work on this agent (9–12) demonstrates the types of preclinical information that can and must be gathered to meet the ethical standards that should be raised by any bona fide human studies committee.

The thesis of the opposing commentary suggests that there is no useful homology across species in the biochemistry and pharmacology of the mammalian spinal cord. There is ample evidence published in this and other journals that proves the contrary. Animal studies stand as the bulwark between the random administration of drugs to humans and are the only way in which the actions of an agent at the systems levels can be assessed before its use in humans. Even when no deficit is shown after a given drug treatment in the animal, we must proceed cautiously. When, on the other hand, deficits are seen, this is a warning that requires our unhindered scrutiny and one we ignore only at our patients' peril. What do we say to the postoperative pain patient receiving spinal somatostatin: that at least seven animal studies with this agent have shown evidence of spinal nucleolysis and/or paralysis; that there are possibly differences in the human and animal effect, but as we do not know the mechanisms of that lesion, we cannot absolutely exclude local toxic actions in humans? Is this what the human studies committees at the several institutions that have approved the use of somatostatin in nonterminal patients required? What were their questions on these issues? Were they aware of even the preliminary data reported by Dr. Chrubasik himself that paralysis and death occurred in his rodent studies (1)? If so, we would be interested to know how they resolved the relevant issues. Can we anticipate now that such committees no longer function in that oversight capacity?

The irony of this situation is that the efforts of Dr. Chrubasik to write letters and carry out clinical trials in the absence of making a scientific effort to understand the issues of toxicity have done more to impede the eventual clinical examination of this agent than anything that our laboratory has done. Letter-writing such as this is a noisome task, but one should not remain silent while others proclaim unsubstantiated opinions and proceed with what may be considered as a premature call for extensive clinical trials in postoperative patients.

Given indicators of the possible utility of a drug, what must be done? Define the neuropathology in systematic chronic drug-dosing animal trials with blinded histologic assessment. If there is toxicity, determine the mechanisms of toxicity. Establish that that mechanism (e.g., effect on vessels, route of metabolism) does not apply in humans. Initiate extensive open trials in terminal cancer patients in whom other therapeutic modalities have failed. Establish the therapeutic index; and *then* call for postoperative pain trials.

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LETTERS TO THE EDITOR

ANESTH ANALG
1990:70:222-9

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Cardiac Arrest and Mitral Valve Prolapse

Key Words: HEART, ASYSTOLE—mitral valve prolapse.

To the Editor:

The recent report by Abraham and Lees (1) of cardiac arrests after needle puncture in a patient with mitral valve prolapse (MVP) is intriguing. However, the diagnosis of MVP in their patients does not appear to be clear-cut. The authors mention that history and physical examination revealed no abnormal cardiac findings. The diagnosis of (mild) MVP was apparently based solely on echocardiographic findings. The echocardiographic criteria for such a diagnosis were not mentioned. As is well known, false-positive diagnosis of MVP is frequent on both M-mode and two-dimensional echocardiography (2). This is particularly true when there are no physical findings of MVP, e.g., midsystolic click and/or late systolic murmur (3). Women with MVP are usually tall and slender (2,4). Their patient, a 70-kg woman 160 cm tall, hardly fits the type.

Both episodes of cardiac arrest in their patient were preceded by progressive sinus bradycardia. Simple vasovagal syncope is the most likely explanation. I agree with the authors' suggestion implicit in the title of their article that it is psychogenic in origin. Although it is true that patients with MVP have increased levels of anxiety, their patient's problem does not seem to be connected with MVP, which she most likely did not even have.

Mitral valve prolapse is a very common condition, occurring in 1%–38% of the general population (5). It is generally a benign condition (6); sudden death is rare (7). To advocate monitoring, intravenous access, immediate availability of resuscitative equipment and medication, and preoperative anticholinergic and sedative administration before every needle puncture in patients suspected or diagnosed as having MVP is hardly justified.

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In Response:

Dr. Cheng's letter indicates an in-depth understanding of MVP. However, he raises three points that should be addressed.

First, did this patient have MVP? Dr. Cheng's assertion that history and physical examination revealed no abnormal cardiac findings is incorrect. As stated in the case report, this patient did have a 3-mo history of occasional chest pain, which is considered a symptom of MVP and which had been previously attributed to MVP as diagnosed by echocardiogram. Mitral valve prolapse was again found on echocardiogram subsequent to the two cardiac arrests. Whether or not this patient's chest pain was in fact due to MVP is unclear. Also, the possibility of a false diagnosis of MVP is possible, although this false diagnosis would have then occurred twice, i.e., before and after the cardiac arrest.

Second, was the arrest secondary to MVP or was it vasovagal? Although the two episodes of cardiac arrest may have been primarily vasovagal in origin, as they were both preceded by progressive sinus bradycardia, vasovagal activity to the point of complete cardiac arrest is most unusual. A predisposition to such an extreme vagal reaction in a patient with preexisting MVP would appear possible, as MVP patients do have an increased incidence of arrhythmias.

Most important, Dr. Cheng states "To advocate monitoring, intravenous access, immediate availability of resuscitative equipment and medication, and preoperative anticholinergic and sedative administration before every needle puncture in patients suspected or diagnosed as having MVP is hardly justified." We do not advocate this for every patient with MVP, before every needle puncture. We do, however, advocate that "regional anesthesia" in patients with MVP not be undertaken without these precautions. Regional anesthesia (in this case an intended epidural block) is not equivalent to a mere needle puncture, neither in the physiologic consequences nor in the emotional responses elicited.

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Book Reviews

Diagnosis and Management of Arrhythmias Volume 7, No. 2 of Anesthesiology Clinics of North America

S. J. Thomas, ed. Philadelphia: W. B. Saunders, 1989, 224 pp, \$28.00.

"Arrhythmias, arrhythmias, what's the big deal? A little lidocaine here, . . . a zap or two and all will be well," begins the editor's preface to this recent issue of Anesthesiology Clinics. This reviewer finds the implication that anesthesiologists care little about cardiac physiology or pharmacology and that we are "not sure what it has to do with treating real people" objectionable. Luckily, the individual contributors have chosen to present detailed and largely accurate summaries dealing with the etiology, diagnosis, and therapy of intraoperative arrhythmias. Considering the complexity of the data presented, all nine chapters are extremely well written and very readable. The reader of this volume will definitely have an improved understanding of dysrhythmias in the perioperative period

There are several deficiencies in the monograph. Although some topical overlap is unavoidable in a multiauthored text, redundancy concerning basic mechanisms of arrhythmogenesis and cellular electrophysiology is excessive for a volume of this length. The book is well edited, and few errors were found. However, many of the figures are poorly labeled—with identifying arrows or letters missing, for example. The index at the conclusion of the volume is quite poor with little cross-referencing, several omissions of important material, and a few errors. The index is poor enough to limit the usefulness of this book as a later reference source.

The chapter on basic electrocardiology is a good review of the subject. Eight pages, unfortunately, are devoted to the electrocardiogram during myocardial ischemia, a subject well covered in other texts. Surprisingly, the relationship between ischemia and arrhythmias, and mechanisms for arrhythmias during ischemia are not discussed. The chapter on etiology is extensive and well written. Table 1, "Causes of Arrhythmias," at first glance seems frightfully complex, but is well explained in the text. The chapter on recognition of ectopic beats is interesting. On page 318, I believe authors Royster and Roberti have confused the term "delayed after depolarizations" with "late potentials" determined noninvasively by signal averaged electrocardiograms. The latter represent areas of slowly conducting myocardium previously damaged by ischemia or cardiomy-

opathy, which form the substrate for reentrant ventricular tachycardia, not triggered automaticity. The recommendations given for managing dysrhythmias at the end of the chapter, although interesting, are not proven. The authors, for example, state that lidocaine should be combined with procainamide therapy as combinations of type 1A and 1B drugs may be more effective than either drug alone. The reference given, however, deals with oral administration of quinidine and mexiletine (1) and may relate more to drugs binding to different physical states of the sodium channel (i.e., open, closed, or inactivated) than the specific drug type. The chapters on narrow and wide complex tachycardias are well written, except for the discussion of preexcitation syndromes. In an effort to conserve space Herschman and Kaufman have neglected to explain that the specific arrhythmia noted in a patient with Wolff-Parkinson-White syndrome determines drug therapy. The chapter by Ross and Martins was a high point of the book with fine discussions of bradydysrhythmias and atrioventricular block. The chapter on arrhythmias in children makes for interesting reading. The discussion of management of Wolff-Parkinson-White syndrome in the pediatric patient is excellent. Figure 1, an M-mode echocardiogram designed to show fetal atrial tachycardia in utero, is small and poorly labeled. On page 408 the authors describe drug doses for digitalization, but incorrectly refer to "digitalis" instead of "digoxin." Luckily, this erronous information was not indexed so the reader is unlikely to use it later. The chapter on pharmacologic treatment provides the usual discussion based on the Vaughan Williams classification (2). It is unfortunate that the chapter was written before indications for flecainide and encainide were changed due to the high incidence of sudden death associated with their use. The chapter is noteworthy for an excellent discussion of the use of verapamil in patients with Wolff-Parkinson-White syndrome. Unfortunately, this discussion is not referenced in the index. Parenthetically, the discussion of adenosine should have mentioned that in Europe the formulation commonly used is "Striadyne," which contains adenosine triphosphate that is rapidly broken down to adenosine. Zaidan's chapter on electrical treatment begins with a discussion macro versus micro of reentry. This reviewer disagrees with his description of reentry and believes that he is really describing single versus multiple wavelets of reentry. When discussing the pacemaker therapy of ventricular tachycardia by overdrive pacing, Zaidan fails to mention that acceleration of ventricular tachycardia is common and that immediate facilities for defibrillation must be available. The instructions for activation and inactivation of the AICD implantable defibrillation are extremely timely and very useful to any anesthesiologist who may see these patients in emergency surgery.

Despite some limitations the book is well written and covers the field well. It is recommended for reading by all anesthesiologists, with one caution that its later use as a reference text will be limited by the poor index.

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Techniques of Regional Anesthesia D. B. Scott. East Norwalk, Conn.: Appleton & Lange, 1989, 221 pp, \$85.00.

In the preface it is stated that this book is intended to serve as a "comprehensive volume of regional anesthetic techniques, . . . to provide an up to date text, and to include as many techniques relevant to modern practice as possible." The content and design of this book are similar to that of the Illustrated Handbook in Local Anesthesia (1979), which was a collaborative effort edited by Ejnar Eriksson, MD, and illustrated with anatomic drawings by the present artist, Poul Buckhoj. The beautiful drawings of Poul Buckhoj will be familiar to those in the field of regional anesthesia from his work in other recent productions from the same publisher.

The book is indeed comprehensive in its description of regional anesthetic techniques, opening with a 30-page introduction, followed by individual sections covering topical anesthesia, local infiltration, peripheral nerve block, central neural blockade, sympathetic nerve blockade, and a final section on postoperative pain relief. In each section, individual neural blockade procedures are described with respect to anatomic relationships and landmarks, patient positioning, technique, suggested drugs and dosages, and potential complications. On the facing page, numerous photographs, photoradiographs, anatomic drawings, and diagrams are provided to illustrate the description provided by the text.

The introduction attempts to provide the reader with an overview of the use of local or regional anesthesia, pre- and postprocedure patient management, pharmacology of local anesthetic and adjuvant drugs, complications and their management, and aids to regional anesthesia. This section should provide the novice with basic information relating to the practical management of patients for regional blockade procedures. In the opinion of this reviewer, however, the discussion of the pharmacology of local anesthetic and other

drugs is oversimplified, at times to the point of providing misinformation, as in the statements "Local anesthetics have pKa's above 7.4 and the greater the pKa, the greater the amount of uncharged form that is present," and "methoxamine is an alpha-receptor agonist and a beta-blocker." A clear, thorough discussion of local anesthetic pharmacology appears to be beyond the scope of this publication.

The sections describing the various neural blockade procedures are written in a well-organized manner with adequate information and illustrations to provide a reasonably thorough understanding of the technique. It was the author's intention to provide a description of only one technique for the various procedures, and for the most part, the techniques described are those most commonly used in modern practice. The procedures described throughout the various sections range from the more common, such as subarachnoid, epidural, and brachial plexus blockade, to the more esoteric, such as cervical plexus and trigeminal ganglion blockade procedures. An extensive section is provided describing various neural blockade procedures of the head and neck, including dental and ophthalmic anesthetic procedures. The comprehensive nature of this text with respect to the procedures described makes it a valuable reference for both the novice and the more experienced anesthetist.

The section on postoperative pain management briefly discusses the use of regional blockade procedures for postoperative analgesia. Although brief, this section does provide an introduction to this application of regional blockade techniques. The use of epidural and intrathecal opioid analgesia is also mentioned, but without sufficient information to provide the reader with an adequate description of the principles and practice of spinal analgesia in postoperative pain management.

Single authorship of this publication does provide the intended consistency of style. The reader must be reminded, however, that the information published in this format is not the product of peer-review and statements may reflect the bias of the author without support in the scientific literature.

In summary this publication provides a clear description of the wide variety of regional blockade techniques used in modern practice, and is complemented by photographs and the drawings of Poul Buckhoj, which are unsurpassed in beauty and anatomic correctness. This text is representative of the quality associated with the other similar productions of the same publisher. Although this work is not recommended as a definitive, comprehensive reference for regional anesthesia, its practical descriptions and illustrations of a variety of neural blockade procedures would be an invaluable addition to the library of teaching institutions and those practitioners with a subspecialty interest in regional anesthesia.

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Introduction to Regional Anesthesia D. B. Scott. East Norwalk, Conn.: Appleton & Lange, 1989, 94 pp, \$24.00.

The purpose of this manual as stated in the preface is to provide a description of "a limited, but reasonably comprehensive, list of techniques" for the practicing anesthetist. This publication is a pocket-sized, abridged version of a larger text, *Techniques of Regional Anesthesia*, and is limited to the more common techniques of regional blockade.

This publication opens with the same introductory section as the larger version, followed by descriptions of an appropriate selection of commonly used regional anesthetic techniques, including brachial plexus, sciatic nerve, lumbar plexus, digital nerve, intercostal nerve, and epidural and subarachnoid blockade procedures. There is also a section describing intravenous regional anesthesia. The descriptions of these procedures and the accompanying diagrams, drawings, and illustrations are essentially identical to those found in the larger version of this text. This provides a handy reference for the commonly used procedures with clear explanation of the techniques complemented by the beautiful illustrations of Poul Buckhoj.

This reviewer found the greatest weakness of *Techniques* of *Regional Anesthesia* to be the introductory section, especially with respect to discussion of the pharmacology of local anesthetic drugs. The inclusion of that entire section in this smaller version is questioned by this reviewer. Perhaps a revision or deletion of that section would have been more appropriate. Correction of publication errors in the larger text are noted in this smaller version.

This manual appears to be a valuable source for trainees in regional anesthetic techniques due to the clarity of the descriptions and the abundance of excellent illustrations. As a companion to a reference text for a more in-depth discussion of pharmacology and toxicology of local anesthetic and adjuvant medications, as well as a description of the less commonly used techniques in regional anesthesia, this manual is highly recommended by the reviewer.

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Essentials of Critical Care Pharmacology Bart Chernow, ed. Baltimore: Williams & Wilkins, 1989, 498 pp, \$39.95.

The second edition of The Pharmacologic Approach to the Critically Ill Patient is an important reference work for the intensive care unit. Because the second edition crashed through the \$100 price barrier, few practicing physicians and even fewer trainees have been able to justify adding the book to their personal libraries. Therefore, Chernow and his publishers have "abridged" the second edition in the hope that trainees will find the paperbound book

affordable. But Essentials of Critical Care Pharmacology is not a true abridgment. Entire unabridged chapters have been pieced together to produce this book.

Several excellent chapters have been chosen. Maher's "Pharmacokinetic Alterations with Renal Failure and Dialysis" is probably the most thorough review of the area available anywhere. The chapter includes extensive tables that summarize the changes in pharmacokinetic parameters seen with renal failure, hemodialysis, and peritoneal dialysis for virtually every conceivable medication. Unfortunately, the introductory pharmacokinetics chapter that preceded this chapter in the original book has been omitted in the abridgment. The trainee who does not already possess a firm foundation in pharmacokinetics may therefore find it difficult to apply the information in Maher's chapter as well as the accompanying chapters dealing with the pharmacokinetic effects of other types of organ failure.

Several fine chapters have been included in the abridgment, Freas' "Poisoning" being a notable example. The "Pediatric Pharmacotherapy" chapter contains some very interesting material dealing with drug delivery systems. The chapter dealing with divalent ions is also excellent. However, an equally well-done chapter by the same authors dealing with insulin, oral hypoglycemics, and glucagon has been omitted in the abridgment. Several other fine chapters from the original, including "Glucocorticoids in Sepsis" and "Cerebral Protection," were also not included.

The chapter on vasodilators is first-rate, and the chapter on inotropes is adequate. However, this reviewer prefers a more unified approach to these classes of drugs. Several chapters resemble an undergraduate pharmacology text in their approach. The antibiotic chapter is a particular disappointment. Antibiotics have great potential to benefit or harm the critically ill patient at the chapter provides little insight concerning antibiotic choice in these patients. A facet of clinical pharmacology with wide application in critical care medicine—therapeutic drug monitoring—is not presented in a systematic fashion in either the abridgment or the original.

Essentials of Critical Care Pharmacology has lost most of the continuity of the original book. It should therefore be viewed as a collection of reviews on various topics related to critical care that were written in 1987 and edited in early 1988. The chapters and their references were not updated, so for practical purposes this book is vintage 1988. Although Essentials is soft-covered, it is not compact and does not fill the need for a pocket-sized paperback covering the pharmacology of many of the drugs used in critical care. For these reasons, I cannot recommend Essentials in Critical Care Pharmacology to the anesthesia trainee despite its small price tag.

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The CO₂ Laser in Otolaryngology and Head and Neck Surgery

V. H. Oswal, H. K. Kashima, and L. M. Flood, eds. Boston: Wright, 1989, 200 pp, \$130.00.

The CO2 Laser in Otolaryngology and Head and Neck Surgery is a multiauthored book that attempts to provide a detailed view of all aspects of ENT laser surgery, including anesthesia and physics. In the preface, the editors state that it was their goal that "each chapter should be self-contained and complete in its own right." Therein, in this reviewer's opinion, lies the fatal flaw of this text. There is a separate chapter devoted to anesthetic considerations during laser surgery. This chapter consists of two distinct parts, one from the United Kingdom point of view and the other from the United States point of view. If these were the only discourses on anesthetic technique then the two differing views would provide a refreshing change from the singleauthor perspective to which we have become accustomed in so many other texts. Unfortunately, in this text every author has an opinion as to how anesthesia should be provided, and many of these are conflicting and unsubstantiated by the literature, either cited or implied.

The book claims to be concerned with the CO2 laser, yet Nd-YAG, argon, and KTP lasers are also discussed at some length. This book is valuable to those who are starting to do laser procedures, as a good deal of attention is devoted to laser safety in the operating room, anesthetic considerations, as well as patient and operating-room personnel safety. Almost one-half of the text is devoted to anesthesia, laser operating principles, and safety. The remainder of the book discusses specific lesions and the applicability of laser surgery to these lesions. This reviewer feels that this book, at almost \$1.00 per page of text, is not worth the price. Several reviews have been published concerning anesthesia and laser surgery, and considerations for endotracheal tubes have gone far beyond wrapped red rubber tubes. Tubes are available today that are impervious to the CO₂ laser. The field is changing rapidly, and thus it is no surprise that a book that takes years to produce would be lagging behind current practice. As stated earlier, if you are in the process of setting up a laser facility and specifying safety procedures, this book might be worthwhile.

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Management of Postoperative Pain Volume 7, No. 1 of Anesthesiology Clinics of North America

R. V. Oden, ed. Philadelphia: W. B. Saunders, 1989, 243 pp, \$29.00.

In the last 5 yr there has been considerable interest among anesthesiologists in providing improved control of pain in the postoperative period. Before this time, only scattered members of our specialty used intercostal or continuous epidural nerve blocks with the longer-acting local anesthetics, transcutaneous electrical nerve stimulation, and—rarely—narcotic infusions. Since 1985, the commercial availability of preservative-free morphine solutions for epidural and intrathecal injection and the production of microprocessor patient-controlled analgesia systems have literally meant that effective postoperative pain management is now possible in hospitals of all sizes. Thus there is certainly a place for a new reference text on this topic.

A book on the management of postoperative pain should be organized and written in such a manner so as both to make its clinical information readily accessible and to serve as a relevant source for more in-depth reading. Unfortunately, this new book falls short as a handy clinical reference for everyday use. The individual "articles" are very well-referenced, but the book suffers from a multitude of contributors whose discussions are often redundant in areas such as neurophysiology of pain and the pharmacology of spinal and systemic opioids. Moreover, the clinical uses of the more important drugs and some techniques are not well described or are even ignored. Some of the problems may have been averted by single authorship or perhaps that of a "few" contributors.

The strengths of Management of Postoperative Pain include the well-written preface and first article on the incidence and severity of postoperative pain, both by guest editor Rollin V. Oden, MD. Only by understanding the scope and causes for the problem can we begin to approach its solution. For instance, not only are inadequate doses of parenteral narcotics often ordered but various studies show that the amount of intramuscular meperidine or morphine actually received by patients may average only 25% of that prescribed. Furthermore, patients tended to receive the same amount of drugs whether they perceived their pain as being "severe" or "minimal." The article on "Patient-Controlled Analgesia" by Paul F. White, MD, is excellent and provides the first helpful comments on clinical guidance (one-fourth of the way through the book). Insight into how we use technology to cover the shortfalls in skilled manpower can be gleaned from Dr. White's statement: "With attentive nursing care, conventional IM therapy can become 'on demand' and may be as effective as PCA." The article on "Spinal Analgesia" by Richard Gregg, MD, is well written and contains valuable guidance on the use of epidural infusions of narcotics and local anesthetic-narcotic combinations with which most clinicians may be unfamiliar. Dr. Gregg, however, gives us little guidance on bolus doses of epidural or spinal narcotics for surgery of various regions of the body or dose modification according to patients' ages despite excellent studies like those of Rene Martin and colleagues (1). The articles on "Postoperative Pain Management in Children," "Analgesia for Post-Cesarean Delivery Pain," and "Organization of an Acute Pain Service: Training and Manpower" also provide subspecialty material of clinical relevance.

Dr. Lee's discussion of "Non-Narcotic Modalities for the Management of Acute Pain" is well written but does not address the use of transcutaneous electrical nerve stimulation, which has enjoyed some popularity in the past. Neither does it help the reader with suggestions of drug dosages and vasoconstrictor additives for "single-shot" or continuous peripheral nerve block techniques. "Psychological Strategies in Acute Pain Management" by Van Dalfsen and Syrjala is interesting for completeness but is beyond the scope of practice of most clinical anesthesiologists and hospital behavioral medicine staffs. The initial articles in this book on systemic opioid analgesics ignore such important topics as the use of specific drugs and doses acutely in the postanesthesia care unit; which drugs are best suited for outpatients; use of narcotics to control shivering; and sedative-hypnotic drugs as adjuvants to narcotics to control acute pain and anxiety. In Dr. Intrurisi's article on "Clinical Pharmacology of Opioid Analgesics," Table 1 lists intramuscular meperidine (Demerol) as having an analgesic duration of "4-5 hours," which is the common clinical problem when this 2-3 h drug is not given frequently enough. Further, Table 2 does not show butorphanol (Stadol) as an example of a κ -agonist, although this is the

most important drug of its kind and is used specifically every day for visceral pain related to surgery on the uterus and fallopian tubes, especially in outpatient procedures.

Those clinicians with a subspecialty interest in acute and postoperative pain control may wish to include this book in their libraries. It will also be valuable as a general reference for students, residents, and others of the pain-control service interested in the development of some of the newer techniques and the organization of a postoperative pain management team. Otherwise, those interested in specific help in beginning to use newer analgesics by the intravenous route, traditional narcotics for spinal administration, or local anesthetics for postoperative nerve blocks will have to seek additional information elsewhere.

Robert Bettinger, MD Department of Anesthesiology The Western Pennsylvania Hospital Pittsburgh, Pennsylvania

Reference

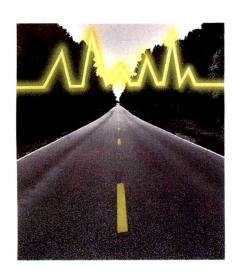
 Martin R, Salbaing J, Blaise G, et al. Epidural morphine for postoperative pain relief: a dose response curve. Anesthesiology 1982;56:423-5.





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Since Trachum has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Trachum than with other muscle relaxants.

during anesthesia may be more common with fractium than with other muscle relevants. Fractium may have prolound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepotarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrohyte disorders or carcinomatosts.

Multiple factors in amesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially tatal hypermetabolic state of skeletali muscle. Halogenated anesthetic agents and succinytcholine are recognized as the principal pharmacologic triggering agents in MH-suscopible patients; however, since MH can devote in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which fractium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, fractium did not trinocor this syndrome. did not trigger this syndrome

Resistance to nondépolarizing neuromuscular blocking agents may develop in burn patients, increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.
The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antiblotics, especially the aminophycosides and polymyxins; lithium; magnesium salts; proceinamide; and quintiline.

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Carcinogenesis, Mutagapasis, Impairment of Fartility: A positive response was observed in the mouse lymphoma. assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

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Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised hen Tracrium is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:

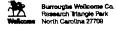
Observed in Controlled Cimical Studies: Wacrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial visal sign changes greater than or equal to 30% observed in 530 patients, without car-diovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of > 0.90 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses < 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately ussers when in userca practices based on canical expenience in the U.S. and the United Kingdom of approximately amillion patients given fractium the following adverse reactions are among the most frequently reported: *Generals* allergic reactions (anaphylactic or anaphylacticid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskelerals* inadecuate, prolonged block; *Cardiovasculae*: hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Plesphratory*: dyspnea, bronchospasm, laryngospasm; *Integrumentary*; rash, urticaria, injection ster reaction.

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¹Payne J: Atracurium. Semin Anesth 1984;3:303-311. ²Basta S, Ali H, Savarase J: Clinical pharmacology of strac depolarizing muscle relaxent. Anesth Analg 1982;61:723-729. of atracurium besylate (BW 33A): A new non-TR-346R



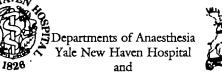
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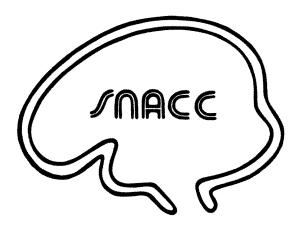
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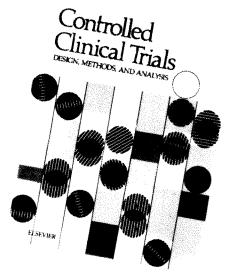
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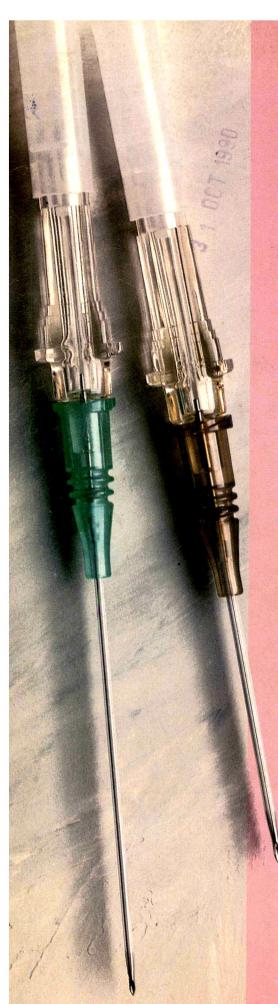
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suffing in increased volume of distribution may contribute to a delay in onset tline, therefore desage should not be

Increased.

Hayoffir Disease: Limited experience in patients with cirmtosis or cholestasis has revealed prolonged recovery time in keeping with the role the fiver plays in Norcuron* metabolism and excretion. Data currently available do not permit desage recommendations in patients with impaired liver function.

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mechanical ventilation has not been studied sufficiently to support design recommendations.

LINDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPPERAL NERVE STUMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

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ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as

UNDER THE ABOYC CONDITIONS, APPROPRIATE BONTOTHERS, SUCH AS USE OF A PERILIPIEAN AND STATES IN UNITED. TO ASSESS THE DESIGNED OF HISTORY PRESIDED FINAL PRINCIPIES IN SERVICE OF THE ADDRESS OF THE ADDRE

anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parentered drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuson® and to minimize the possibility of overdosage, the monitoring of

are attentions of visually for particulate matter and discoloration prior to administration whenever solution and container permit. To obtain macrimum clinical benefits of Morcurors* and to milinifiza the possibility of overdosage, the monitoring of muscle bitton response to peripheral nerve stirrution in a deviser.

The recommended initial dose of Morcurors* is 0.08 to 0.10 mg/kg i1.4 to 1.75 times the ED_{g01} given as an intraverous bolds injection. This dose can be expected to produce good or excellent non-emprency intuition conditions in 2.5 to 3 minutes after injection. Under belanced approximately 25-30 minutes, with recovery to 25% of control achieved approximately 45-50 minutes after injection. In the previous approximately 45-50 minutes, with recovery to 25% of control achieved approximately 45-65 minutes after injection and recovery to 25% of control achieved approximately 45-65 minutes after injection. In the prevence of potenti inhabition and recovery to 25% of control achieved approximately 45-65 minutes after injection. In the prevence of potenti inhabition and the state of inhabition appet or when steady state has been achieved, the latital Morcurors* dose may be reduced by approximately 15%, i.e., 0.086 to 0.05 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Morcurors* (inhabition approximately 15%, i.e., 0.086 to 0.05 mg/kg.)

Prior administration assistanced according to the succinylcholine, a reduction of initial dose of Morcurors* to 0.04-0.06 mg/kg with inhabition anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, unantimizance doses of 0.010 to 0.015 mg/kg of Morcurors* accommended of the initial Morcurors* injection, the first maintenance doses of 0.010 to 0.015 mg/kg of Morcurors* accommended of the initial doses of Morcurors* and the surgical procedures, unantimizance doses of 0.010 to 0.015 mg/kg of Norcurors* according to the patient of the intensity of

movement were near a mission zerou person, 45-ou man arise the instituting cose. Under hatothane anesthesis it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NexCl. 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate	ų.	nfosion Delivery Rate
(μg/kg/min)	0.1 mg/mL*	(mL/kg/min) 0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

10 mg of Norcuron in 100 mL solution †20 mg of Norcuron* in 100 mL solution

The following table is a guideline for mil/min delivery for a solution of 0.1 mg/mil (10 mg in 100 mil.) with an infusion pump. NORCURON® INFUSION RATE - mL/MIN

Amount of Drug	Patient Weight - kg							
μg/kg/min	40	50	60	70 T	80	90	100	
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70	
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80	
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90	
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00	
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10	
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20	
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30	

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Distage in Children: Other children (10 to 17 years of age) have approximately the same design requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a signifity higher initial does and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcurron* on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS (titled Pediatric Use. Information presently available does not permit recommendation on usage in neonstes (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecurorium in children, therefore, no doesing recommendation can be made.

COMPATIBILITY: Norcuror* is compatible in solution with:

0.9% NaCl solution
5% glucose in water

State water for injection
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Use within 24 hours of microtion permit.

8TORAGE: 15-30°C (59-88°F). Protect from fight.

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- References:

 1. Morris RB, Cahatan MK, Miller RD, et al: The curdiovascular effects of vecuronium (ORG NC45) and pencuronium in patients undergroup coronary artery bypass grafting. *Anaesthesisingy* 1883;58:438-440.

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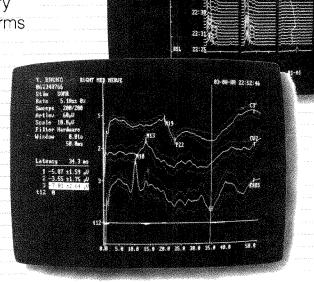
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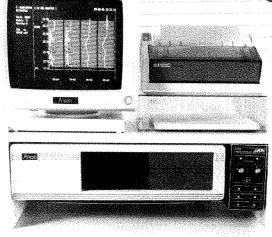
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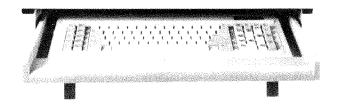
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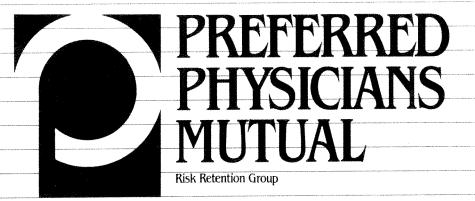
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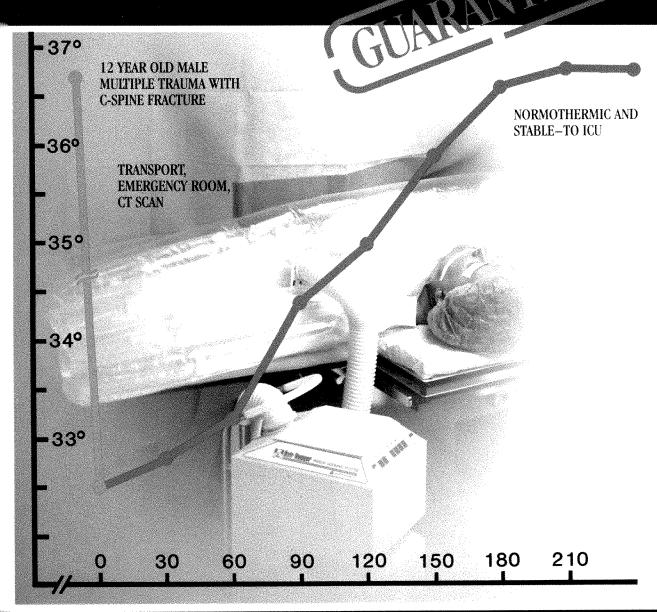
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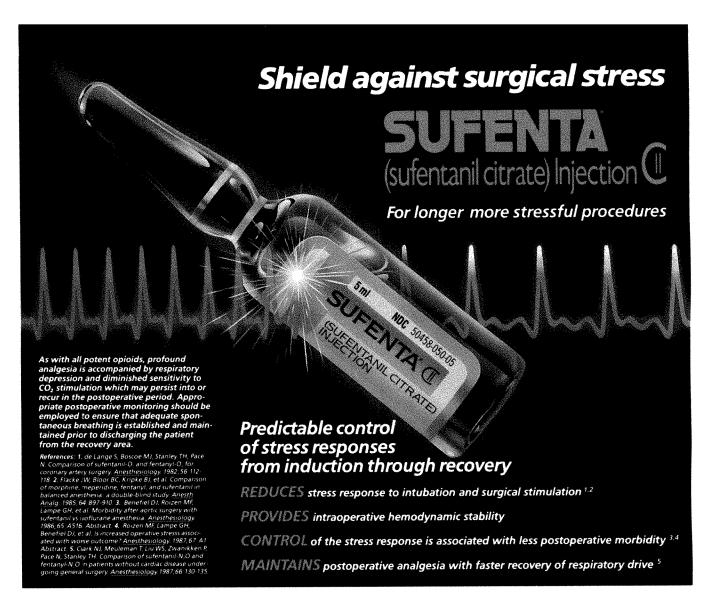


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ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

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of SUFENTA.

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Intragence activity, see AniMAL LUMI, DULOT for reproduction studies in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in or 5 trabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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Contraindicational 'lagamet' is contraindicated for patients known to have inspersensitivity to the product.

unctions: Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagar cimetidine hydrochloride) injection by intravenous bolus.

Symptomatic response to "ligamet" therapy does not preclude the presence of a gastric maligramity. There have been rare reports of transient healing of gastric ulcers despite subsequently documented maligramity.

Reversible confusional states have been observed on occasion, predominantly in severely III patients.

In severy's in putrics. "Regimes" has been reported to reduce the hepatic metabolism of werfarin-type articoagulants, phenyloin, propranoloi, chloridiszepoxide, disepsim-certain tricyclic antidispressants, laboraine, theophyline and metonicistole. Chliciathy significant effects have been reported with the warfarin anti-coagularius; therefore, dose monitoring of protheroidin threis recommended, and adjustment of the anticoagulant dose may be necessary when "Rigianed is administered concomitantly, interaction with phenyloin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

however, a crossover study in healthy subjects recording either "Bigarnet" 300 mg a full. or 800 mg h.s. concombiantly with a 300 mg bild, dosing of the coph, illne (Theo-Dur⁴), key Pharmaceuticals, inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not evaluable, (Note: All patients receiving theophylline should be monitored impropriately, regardless of concombiant drug therapy.)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cal humors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet'.

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Pregnancy Category B: Reproduction studies have been performed in raiss raibbits and mice at doses up to 40 times the normal human dose and have rational and must woost up to the service of the fetus due to 'lagamet'.
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly

Lack of experience to date preduces recommending "ligamet" for use in children under 16 unless anticipated benefits outweigh potential risks; generally nursing should not be undertaken by patients taking the drug since clinedoine is secreted in human milit.

generally nursing should not be undertaken by patients talking the drug since denetione is secreted in human milk.

Authorine Reactilease Diarrhea, dizaless, somnolerice, headache, Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, narice); halluchations, discheritational, predominantly in severely lipscheric, have been reported. Reversible impotence in patients with pathological hypestonetroly disorders receiving Regionet, particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale someliame studies at regular doses has not exceeded that commonly reported in the general population. Gynecomastic has been reported in patients travalled for one month or longer. Decreased white blood cell counts in Tagemet'-brauted patients (approximately 1 per (2000) patients, including agranulocytosis (approximately 3 per million patients), have been reported including agranulocytosis (approximately 3 per million patients), have been reported including agranulocytosis (approximately 3 per million patients). Hossis of these reports were in patients who had serious concombant linesses and received drugs and/or travaller and increased some meutropenia. Thrombocytogenia (approximately 3 per million patients) and, very arrely, cases of absolutional flagmost material increased patient in the patient (approximately 4) per million patients) and (very arrely cases of absolutional flagmost has been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic hepatic receiving Tagemet' has been reported in received patient with pre-ceiving material and alengic reactions, including a manifysius and hypersensibility viscuitis, have been reported. Reversible and patients with pre-cessing artists and hypersensibility viscuitis, have been reported. Hepatic reported, but no causal resistoration have been resported, but no causal resistoration have been resported, but no causal resistoration have been resported, but no causal resistoration

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Frank W. Karistack R. Rockhold F, et al. Comparison between continuous and insemitient infusion regimens of cheeldine in user patients. Cfill Pharmacol The 1899;46:247-237. & Costo MJ. Russel J. A. Soolin SJ. et al. Control of gastric pH with clinecidine: Boluses versus primed Infusions. Gastroenterology 1985;97:532-537. B. Baptista RJ. Role of histamine Info-Jecopton managorists in total parenteral nutrition patients. Am J Med 1987; Böljsuppi 6 AJ-53-57.

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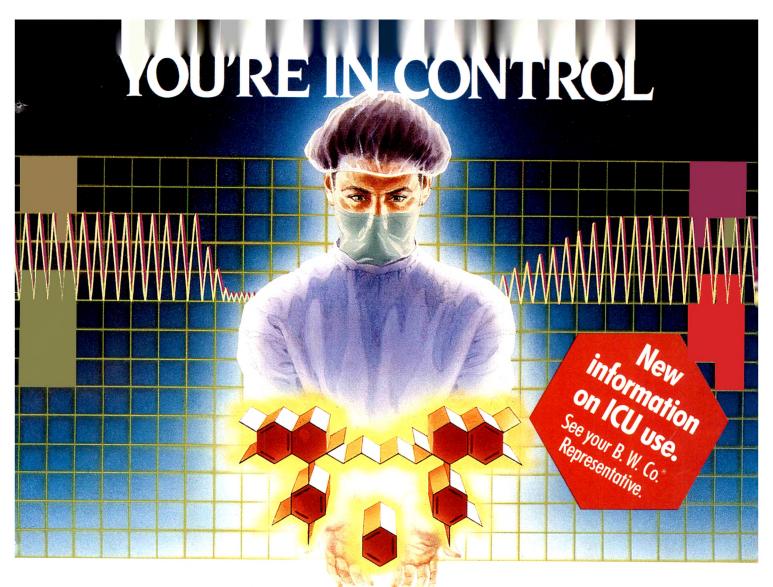
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TRACRIUM* (atracurium besylate) INJECTION

Brief SummaryThis drug should be used only by adequately trained individuals familiar with its actions, characteristics, and

hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYSEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with ade

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solu-tions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

Tracrium Injection 10 mt, multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes tatal Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS:

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will be countered the bracker and inconverted the many anaptients of the recommended dosage range. It will be countered the bracker and in the recommended dosage range. It will be a described to the countered the bracker and the recommended dosage range.

Since Tractium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with fractium than with other muscle relaxants.

Tractium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarzing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially latal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinyteholine are recognized as the principal pharmacologic triggering agents. The clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which fractium has been used. In studies of MH-susceptible patients, fractium dio not trigger this syndrome.

Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma.

Lang-Term Use in Intensive Care Unit (ICU): Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered.

blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) infravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is with enterpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolities following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurance, isoflurane, haldmane, certain antibiotics, especially the aminoglycosides and polymyxins, lithium; magnesium salts, procamanide, and quinidine.

salts; proceinamide; and quinidine.
If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect

should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may in

crease the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

a patient has recovered from succinvincement-induced neuromuscular blockade. Carcinogenesis, Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. Pregnancy: *Teratogenic Effects*: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Fractium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to fractium in any of the newborn infants, although small amounts of fractium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and fractium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when fractium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:

ADVERSE REACTIONS:

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials.

Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Important adverse reactions was 7/875 or 0.8%

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 5.0 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported. **General* allergic reactions (anaphylactic or anaphylacticid) which, in rare instances, were severe (e.g., cardiac arrest); **Musculoskeletal inadequate, prolonged block, **Cardiovascular* hypotension, vasoditation (flushing), tachy-cardia, **Paspiratory** dyspnea, bronchospasm, laryngospasm; **Integumentary** rash, urticaria, injection site reaction.**

STORAGE: Tractium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tractium Injection within 14 days even if rerefrigerated.

Miller R, Rupp S, Fisher D, et al. Clinical pharmacology of vecuronium and atracurium. *Anesth* 1984;61:444-453. Payne J: Atracurium, In Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*. Orlando, Grune & Stratton. 1984, p. 98.

Eagar B, Flynn P, Hughes R: Infusion of atracurium for long surgical procedures. Br J Anaesth 1984;56:447-452



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Continuous Intercostal Blockade With Lidocaine After Thoracic Surgery

Clinical and Pharmacokinetic Study

D. Safran, MD, G. Kuhlman, MD, E. E. Orhant, BS, M. H. Castelain, MD, and D. Journois, MD

SAFRAN D, KUHLMAN G, ORHANT EE, CASTELAIN MH, JOURNOIS D. Continuous intercostal blockade with lidocaine after thoracic surgery. Clinical and pharmacokinetic study. Anesth Analg 1990;70:345–9.

The efficacy and the side effects of a continuous infusion of lidocaine in the fifth intercostal space for the management of postoperative pain after lateral thoracotomy were evaluated in 20 adults. An indwelling catheter was inserted in the appropriate intercostal space before thoracotomy closure. After recovery from general anesthesia, a loading dose of 3 mg/kg of 1.5% lidocaine with epinephrine 1:160,000 was injected through the catheter, followed by a continuous infusion of 1% lidocaine without epinephrine at a rate of 1 $mg \cdot kg^{-1} \cdot h^{-1}$ for 54 h. In seven patients pharmacokinetic data were obtained. Pain, assessed by visual continuous analog scale, decreased from a median score of 8 (range, 7-10) to a score of 5 (range, 2-7) 20 min after the loading dose of lidocaine and continued to decrease until the end of the study (P = 0.0001). Complete cutaneous analgesia, assessed by pinprick test, was seen in a median of three thoracic spinal segments (range, 0-6) with partial cutaneous analgesia in seven segments (range, 6–9) 40 min after the loading dose, and levels that remained unchanged for 54 h (P=0.0001). Peak lidocaine serum concentrations, $1.9\pm0.7~\mu g/mL$, were present 9 ± 3 min after injection of the loading dose. Serum concentrations of lidocaine under steady state conditions averaged $4.8\pm0.9~\mu g/mL$ (range, $3.5-5.8~\mu g/mL$). This level under steady state conditions, though below the toxic level, suggests that additional bolus injection of lidocaine during the course of infusion might result in potentially toxic serum levels of lidocaine. Our data show that the intercostal infusion of lidocaine in a single intercostal segment after thoracotomy provides prompt, prolonged, and effective analgesia, without side effects and with a pharmacokinetic profile indicating that serum levels remain below toxic threshold values.

Key Words: PAIN, POSTOPERATIVE—continuous intercostal block. ANESTHETIC TECHNIQUE, REGIONAL—intercostal block, continuous. PHARMACOKINETICS, INTERCOSTAL BLOCK—lidocaine. ANESTHESIA, THORACIC—postoperative pain.

Intercostal nerve blockade (INB) using an injection of large volumes of local anesthetic solution into a single intercostal space has an established role in providing analgesia over an extensive field for upper abdominal and thoracic surgery. Successful maintenance of widespread INB over a prolonged period by insertion of a catheter to an intercostal space with repeated "top-up" doses of local anesthetic has been reported in patients with multiple rib fractures and after cho-

lecystectomy and cardiac surgery (1). Nevertheless, the pharmacokinetics of such injections has not yet been studied, and analgesia is not really continuous, as "top-up" injections are performed "on demand," when patients consider their degree of analgesia to be inadequate. The continuous infusion of local anesthetic through an intercostal catheter might, however, provide continuous, effective analgesia. The safety of such a technique deserves pharmacokinetic evaluation in view of the important vascular absorption of local anesthetic injected intercostally (2).

We therefore evaluated the efficacy, side effects, and pharmacokinetics of a continuous intercostal infusion of lidocaine into a single intercostal space over a period of 54 h in adults after lung resection.

Received from the Département d'Anesthésie et de Réanimation Chirurgicale Necker-Enfants Malades-Laënnec (Pr G. Barrier), Hôpital Laënnec, Paris, France, and the Département d'Anesthésie et de Réanimation Chirurgicale (Pr K. Samii), Hôpital Bicêtre, Bicêtre Cedex, France. Accepted for publication November 27, 1999

Address correspondence to Dr. Safran, Département d'Anesthésie, Hôpital Laënnec, 42 rue de Sèvres, 75007 Paris, France.

Patients and Methods

After institutional approval and each patient's written informed consent, 20 patients scheduled for pulmonary resection under unilateral thoracotomy were studied.

The patients, 17 men and 3 women, ASA physical status I through III, aged 33–65 yr, (mean \pm sp = 54.3 \pm 9.9), weighing 51–95 kg (68.2 \pm 13 kg), underwent a standard posterolateral thoracotomy for lung resection through the sixth intercostal space without costectomy.

After premedication with intravenous midazolam (0.1 mg/kg), anesthesia was induced with thiopental (6 mg/kg) and fentanyl (3 μ g/kg). Tracheal intubation with a plastic Robertshaw double-lumen catheter was performed with the aid of pancuronium (0.08 mg/kg). An arterial cannula was inserted for monitoring systemic arterial pressure and blood sampling. Anesthesia was maintained in the lateral decubitus position with 50% N₂O/O₂, 1.4% end-tidal concentration of enflurane, and further increments of fentanyl. Fentanyl was discontinued at least 60 min before the end of surgery.

Toward the end of surgery and while the thorax was still open, a Portex epidural catheter was inserted by the surgeon through an 18-gauge Tuohy needle, posteriorly and percutaneously into the fifth intercostal space (just below the surgically opened interspace). After inserting the needle 3 cm through subcutaneous tissue, the tip of the needle was placed in the fifth intercostal space, close to the lower border of the upper rib and directed toward the midline, in such a way as to leave the tip of the catheter 8 cm from the posterior midline after removal of the needle. Correct placement of the catheter was ensured visually and by palpation; aspiration through the catheter and injection of 5 mL of methylene blue into the catheter assured that the tip of the catheter lay neither in the pleural cavity nor in the subarachnoid space. The catheter was firmly fixed to the skin, and a micropore filter was attached.

After recovery from general anesthesia, analgesia was achieved in the recovery room by the injection through the catheter of a bolus of 3 mg/kg of 1.5% lidocaine with epinephrine 1:160,000. This was immediately followed by the continuous infusion of 1% lidocaine without epinephrine at the rate of 1 mg· kg⁻¹·h⁻¹ with the patients in semisitting position, which is our routine postthoracotomy position for the first day. This infusion was discontinued at the end of the study, 54 h after the bolus injection of lidocaine. No additional analgesic drug was to be administered unless the patients specifically asked for it.

Clinical Assessment

The electrocardiogram (V₅ lead), heart rate, and systolic and diastolic arterial blood pressures were monitored throughout the study. Arterial blood gas tensions were measured immediately before the first intercostal injection of lidocaine and then every 3 h.

Pain was quantified using a continuous visual analog 0-10 scale (VAS). The level and extent of cutaneous analgesia measured by pinprick was classified as "complete analgesia," "partial analgesia," or "no analgesia" before (T₀), and 20, 40, and 60 min after, and 3, 6, 18, 30, 42, and 54 h after the loading dose of lidocaine. At the same times, the ability to cough was scored 0 (unable to cough), 1 (ineffective cough), or 2 (effective cough).

An anteroposterior chest x-ray was taken upon arrival in the intensive care unit, 6 h later, and then every 12 h.

Pharmacokinetics

Arterial blood samples from patients numbered 1 to 7 were drawn into siliconed glass tubes for assay of lidocaine concentration before (T_0) , and 1, 5, 10, 15, 20, 30, 40, and 60 min after, and 2, 3, 6, 18, 30, 42, and 54 h after the loading dose of lidocaine. After centrifugation, the serum was kept at -18° C until analyzed for lidocaine levels. These were measured using gas chromatography after a single extraction in toluene with etidocaine as internal standard (3,4). The chromatograph (Varian 3400) was equipped with a nitrogen-specific detector and a 3-m × 2-mm ID glass column fitted with 3% OV 11 on 100/120 mesh chromosorb W (AW/DMCS).

Noncompartmental analysis was used. The following parameters were estimated: maximum peak concentration after the bolus injection (C_{max}) ; the time to reach the peak (T_{max}); and steady state concentrations (C_{ss}), calculated as the mean of observed concentrations at 18, 30, 42, and 54 h. Total body clearance (CL) was calculated as

$$CL = \sum_{i=1}^{n} (X_{o_i}/C_{ss_1})n,$$

where X_0 is the rate of infusion (amount/time), C_{ss} is the corresponding measured concentration, and n is the number of concentration-time data (n = 4).

Statistical Analysis

Statistical analysis of the clinical results was performed using a Macintosh II computer and Statview

<u>Table 1</u>. Evolution of Clinical Variables: Pain (visual analog scale [VAS]) Scored 0 to 10 and Extent of Cutaneous Analgesia Before the Bolus Injection (T_0) , Then During Infusion

	Time of evaluation									
	T _o	20 min	40 min	60 min	3 h	6 h	18 h	30 h	42 h	54 h
VAS	710	27	3–7	2–7	1-4	2-5	2-4	0-4	0-4	0–3
Total analgesia (n dermatomes)	0	06	0–6	0-7	0–7	1–7	0–7	0–7	0–6	0–6
Partial analgesia (n dermatomes)	0	4–9	6–9	6–10	6–10	· 7–10	5–10	510	4-9	4–9

II software. Analyses of analgesia levels, VAS, and coughing among the different times of the study were made by χ^2 contingency test. A P value <0.05 was considered sufficiently significant to allow rejection of the null hypothesis. Results are presented as median values with ranges.

For pharmacokinetics, analysis of variance for repeated measures was used to determine of there were any significant changes in serum lidocaine levels between hour 18 and hour 54. Results are presented as mean \pm sp.

Results

Clinical Study

The mean duration of surgery was 180 ± 45 min. The mean total dose of fentanyl administered during surgery was $303 \pm 33 \,\mu g$, or $4.4 \pm 0.04 \,\mu g/kg$.

The mean dosage administered for the bolus of lidocaine was 204.3 \pm 39.8 mg, and the volume of injection was 13.6 \pm 2.6 mL. The mean amount of lidocaine infused was 67.9 \pm 13.2 mg/h, and the mean flow rate was 6.8 \pm 1.3 mL/h.

Neither procedural complications nor anesthetic side effects were noticed.

Among the 20 patients, there were no significant changes in Paco₂, heart rate, rhythm, or arterial pressure, even after the bolus injection of lidocaine with epinephrine. The results for VAS and the extent of total and partial cutaneous analgesia at the times of each scoring are shown in Table 1.

The median VAS pain score before lidocaine was 8. It decreased progressively until the end of the study to reach the median value of 2 at hour 54 (P = 0.0001).

The maximum median extent of cutaneous partial analgesia, seven dermatomes (D), was obtained 40 min after the bolus injection of lidocaine in most of the patients (range, 6–9 D). No significant changes were observed until the end of the study (range, 4–9 D). The extent of partial analgesia was greater in a caudad direction than in a cephalad direction (1–4 vs 2–6 D; P < 0.05). The median extent of total cutane-

<u>Table 2</u>. Pharmacokinetics of Lidocaine in Serum After Intercostal Bolus Injection and Infusion

	Weight C,	C _{max}	т 'С		Clearance		
Patient	(kg)	(μg/mL)	T _{max} (min)	(μg/miL)	mL/min	mL·min ⁻¹ ·kg ⁻¹	
1	69	1.9	10	5.8	200	2.9	
2	71	1.4	15	5.6	234	3.3	
3	95	1.5	10	5.3	304	3.2	
4	82	2.2	5	3.7	336	4.1	
5	73	2.0	10	5.6	307	4.2	
6	56	3.5	5	3.6	342	6.1	
7	55	1.2	10	4.3	198	3.6	
Mean	<i>7</i> 2	2.0	9	4.8	274	3.9	
SD	14	0.7	3	1.0	62	1.1	

ous analgesia (3 D) was maximal as early as 40 min (range, 0–6 D) after injection. Thereafter it did not change for the remainder of the study. The extent of cutaneous total analgesia was also greater in a caudad direction than in a cephalad direction (0–3 vs 1–5 D; P < 0.05).

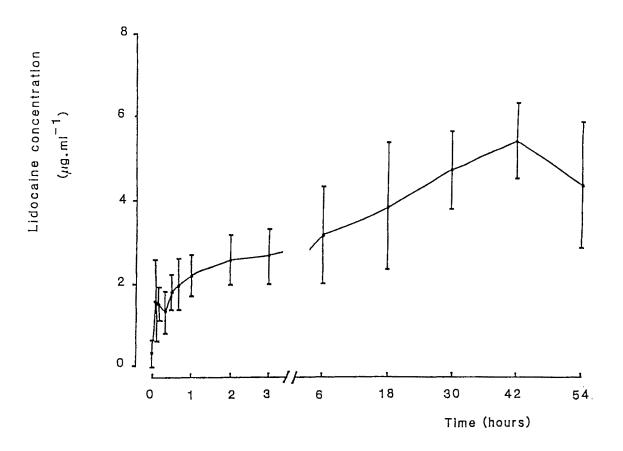
The ability to cough was scored as 0 in each patient before injection. The median score increased continuously with time (P = 0.0001). At the end of the study 14 patients had a score of 1, and 6 patients had a score of 2.

Pharmacokinetics

Parameters calculated from the concentration-time data are presented in Table 2. After the intercostal bolus injection of 3 mg/kg lidocaine with epinephrine 1:160,000, C_{max} was $1.9 \pm 0.7~\mu g/mL$ at 9 ± 3 min. C_{ss} ranged between 3.5 and 5.8 $\mu g/mL$. C_{ss} was not significantly different between 30, 42, and 54 h after injection (Figure 1). Total body clearance was 274 \pm 62 mL/min.

Discussion

A number of studies have shown that INB relieves postoperative pain after thoracotomy and decreases



<u>Figure 1</u>. Serum concentration-time data of lidocaine after intercostal bolus injection and infusion.

narcotic requirements (5,6). Indwelling catheters inserted into the intercostal space can provide longer term and usually more effective block than one-time direct-vision needle block or intermittent percutaneous needle blocks (7).

In previous studies using an intercostal catheter, intermittent "on demand" reinjections of bupivacaine when pain occurs are needed about every 4 h (1,8). We chose to use a continuous infusion after a bolus to achieve a continuous analgesia. Considering the high level of resorption of anesthetic in this way (2) and the lack of data on steady state plasma levels when using intercostal infusion, and because of the potential for cardiac toxicity with bupivacaine, for example, we decided to be cautious and use lidocaine in this preliminary study.

The intraoperative placement of the catheter by the surgeon, while the pleural cavity was still open, appeared to reduce the potential for misplacement, which is probably the most common cause of failure of this technique (9). Under direct vision, we could make sure that the catheter was not lying superficially to the intercostal space, and, upon seeing the spread of the dye under the external pleura, we could

ensure that the tip of the catheter was about 8 cm from midline and out of the pleural cavity.

We did not experience any complications related to insertion of the catheter or the infusion of lidocaine.

Our technique appeared satisfactory, as we obtained a good level and a relatively rapid onset of analgesia. In clinical practice, we could inject the bolus earlier so as to reach a satisfactory level of analgesia at the moment when the patient recovers from general anesthesia. We noticed a progressive decrease of pain up to the end of the study at hour 54 when the catheter was removed. Neither additional systemic analgesics nor "topping-up" doses of local anesthetic solution were necessary. However, it is difficult to evaluate the role of spontaneous decrease of pain between hour 42 and hour 54, and so we cannot define the optimum duration of postoperative infusion

In spite of significant and predictable decreases, VAS never reached 0. Postoperative pain has, of course, several components. Even if incisional pain is relieved, patients undoubtedly experience painful sensations originating from areas uncovered by the block, areas that may be related to visceral afferents, presence of drainage tubes, and discomfort after being in a lateral position on a hard operating table for a long time. These types of pain or discomfort

may require the use of relatively weak systemic or oral analgesics.

Large volumes of solutions injected into one intercostal space, close to the posterior angle of the rib, spread by an extrapleural and paravertebral route to reach several adjacent spaces (9). In our study, pinprick showed that cutaneous analgesia was obtained throughout the whole area of the wound and the number of dermatomes with partial analgesia was about seven. Only one patient had no total analgesia throughout the study except at hour 6 (1 D). Nevertheless, this patient had a range of 6-8 D with partial analgesia every time after the bolus injection. A moderate decrease in the extent of cutaneous analgesia could be expected near the end of the study, and would be related to tachyphylaxis previously described in 20% of cases by Murphy (10). In our study, this phenomenon was observed, but was not statistically significant.

It is noteworthy that in most cases, a spontaneous efficient coughing was not restored.

With respect to the dose and concentration of lidocaine used in our study, C_{max} and T_{max} were in the range of published values for a single-dose injection (11).

After 24 h of continuous infusion of lidocaine, serum concentrations of lidocaine reached a mean C_{ss} of approximately 5 μ g/mL. This concentration may be considered to be below the toxic level as assessed by the lack of clinical signs of toxicity (12). This relatively high concentration is the result of a low clearance value in these postoperative patients (274 \pm 62 mL/ min) as compared with the commonly published values of 800 mL/min. This may be the result of a time-dependent inhibition of lidocaine metabolism, as has been shown after prolonged infusion (4,13). In addition, it has been previously reported that toxic symptoms may relate more to the rapidity of exposure of brain cells to local anesthetic than to the concentration in blood (14,15). Although serum concentration remained below toxic levels in our study, this steady state concentration does not allow additional bolus injections during the course of infusion.

Our results show that INB using continuous infusion of lidocaine is simple and provides prompt, effective, and continuous analgesia after thoracotomy without side effects such as respiratory depression or

hemodynamic changes. The safety of this technique is suggested by the pharmacokinetic data we obtained. Nevertheless, the large extent of cutaneous analgesia obtained suggests that it might be possible to reduce the amount of lidocaine administered, thus improving the safety of the technique, especially in older patients or in those who may be expected to have decreased clearance of lidocaine.

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Echocardiographic Assessment of Mitral Valve Function During Mechanical Cardiopulmonary Resuscitation in Pigs

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HACKL W, SIMON P, MAURITZ W, STEINBEREITHNER K. Echocardiographic assessment of mitral valve function during mechanical cardiopulmonary resuscitation in pigs. Anesth Analg 1990;70:350–6.

Using two-dimensional and M-mode echocardiography, mitral valve function was assessed during mechanical cardiopulmonary resuscitation (CPR). In 10 anesthetized pigs CPR began 1 min after induction of ventricular fibrillation; in all pigs three different compressive forces (200, 350, and 500 Newton [N]) were applied in randomized sequence for 3 min each, thus resulting in a reduction of anterior-posterior chest diameter by 15%, 20%, and 25%, respectively. Echocardiographic recordings of adequate technical quality were obtained from seven animals. During ventricular fibrillation, mitral valve leaflets showed fibrillatory movements without closure. During CPR sys-

tole with a compressive force of 200 N, the mitral valve closed in 114 of 700 CPR cycles (16%). This rate increased significantly (P < 0.001) to 399 of 584 cycles (68%) with 350 N, and further to 470 of 494 cycles (95%) with 500 N. The higher mitral valve closure incidence was linked to statistically significant increases in systolic cerebral (+125%) and diastolic myocardial perfusion pressures (+136%) and cardiac output. We thus conclude that with low compressive force blood flow during mechanical CPR is due mainly to the chest pump mechanism, whereas the cardiac pump mechanism is effective with high compressive forces.

Key Words: HEART, CARDIOPULMONARY RESUSCITATION. MEASUREMENT TECHNIQUES, ECHOCARDIOGRAPHY.

The mechanism of forward blood flow during cardiopulmonary resuscitation (CPR) may be either direct cardiac compression ("cardiac pump mechanism") with closure of the mitral valve and subsequent emptying of the left ventricle (1-4), or an increase in intrathoracic pressure ("chest pump mechanism") with the heart acting as a passive conduit (5-9). As there are numerous investigations supporting each theory, both mechanisms are probably effective under certain circumstances, and the controversial results of previous studies may be due either to differences in the chest geometry of the animals studied or to different CPR techniques. The objective of this study was to test the hypothesis that chest compressive force is a major determinant of the governing of blood flow during CPR; mitral valve function, therefore, was visualized during mechanical CPR with different chest compressive forces.

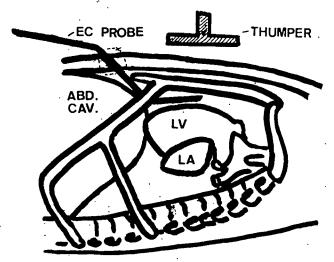
Methods

Animal Preparation

Ten healthy pigs, mean body weight 22 kg (range, 19-24 kg), mean age 9 wk (range, 8-10 wk), were anesthetized with ketamine (20 mg/kg IM) and thiopentone (10 mg/kg IV). After endotracheal intubation the animals' lungs were ventilated at an F102 of 0.35 with the tidal volume adjusted to maintain Pco2 in a range between 35 and 45 mm Hg (Draeger Pulmolog). Ketamine (6 mg·kg⁻¹·h⁻¹), pancuronium (0.3 mg· $kg^{-1} \cdot h^{-1}$), and Ringer's solution (5 mL·kg⁻¹·h⁻¹) were administered continuously throughout the instrumentation and study periods. An epidural pressure transducer (Gould P 50) was positioned over the left brain via a burr hole. The pigs were then placed on a plastic foam bed and remained in the supine position throughout the study. Aortic and central venous catheters were inserted through the femoral vessels. A pulmonary artery catheter (Gould 5F) and a pacing wire (USCI PT 5651) were introduced via the

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<u>Figure 1</u>. Diagram demonstrating the position of the echocardiography probe. LV, left ventricle; LA, left atrium; ABD. CAV., abdominal cavity.

external jugular vein. The common carotid artery was exposed and an electromagnetic flow probe (Gould Flo-probe TM) attached. To facilitate defibrillation (Hellige Servocard) copper pads were fixed subcutaneously in the right and left chest wall. End-tidal CO₂ was monitored continuously at the end of the endotracheal tube (Draeger Capnolog). An esophageal echocardiography transducer (Hewlett-Packard 77020 AC, transducer frequency 5 MHz) was inserted precordially into the anterior mediastinum via an infrasternal incision (see Figure 1).

Cardiopulmonary Resuscitation Technique

Ventricular fibrillation was induced by electric stimulation (35 V, 50 Hz AC) via the pacing wire. External CPR was performed with a microprocessor-controlled pneumatic piston designed to enable adjustment of compressive force between 0 and 1000 N at a rate of 60/min with interposed ventilations (12/min, duration of inspiration 1.5 s). The velocity of compression was held constant and a duty cycle of 50% was chosen. Compressive force was measured by a force transducer (Hottinger-Baldwin U2A) placed between the thumper plate and the chest wall. Sternal displacement was estimated using a graded scale attached to the sternum of the pigs and was corrected for the inevitable molding of the chest occurring with compression.

Data Acquisition

Aortic, pulmonary arterial, right atrial, and epidural pressures were registered continuously on an 8-

channel recorder (Gould 2800) along with common carotid artery flow, end-tidal CO₂, and compressive force. All intravascular pressures were calibrated to room air at mid heart level. The epidural transducer was zeroed off line The flow probe was calibrated using "zero-flow" in vitro (0.9% saline solution). Calibration to electric zero was performed with the probe in situ. Gain calibration as well as offset position were checked immediately before and after each experiment. Cerebral perfusion pressure (aortic pressure minus epidural pressure) and myocardial perfusion pressure (aortic pressure minus right atrial pressure) were calculated off line. The echocardiographic signals (two-dimensional as well as M-mode) were recorded continuously on video tape along with aortic pressure tracing. These tape recordings were used for a cycle-to-cycle assessment of mitral valve performance. Mitral valve movements were judged assessable when high quality images of both mitral leaflets were obtained. Two-dimensional echocardiography was used to confirm that M-mode echocardiographic sampling was performed at the valve level, and M-mode images were then used to assess mitral valve closure.

Study Protocol

In all pigs, instrumentation was followed by a steadystate period of 60 min; blood gas tensions, as well as serum electrolyte, glucose, and lactate levels were analyzed to verify a stable physiologic condition. After registering control data, ventricular fibrillation was induced. Fio₂ was adjusted to 1.0, and conventional CPR began 1 min later. The compressive force was changed every 3 min; 200, 350, and 500 N were applied in randomized order (latin square design). The force on the pneumatic piston device was altered based on the reading of the force transducer. Epinephrine (20 µg/kg) was administered intravenously whenever the compressive force was altered. All pressures as well as carotid flow and end-tidal CO₂ were evaluated 2 min after each change. Ten minutes after induction of ventricular fibrillation (1 min of no flow, 3×3 min of CPR with different compressive forces), another dose of epinephrine (20 μ g/kg) was administered and defibrillation attempted. Cardiopulmonary resuscitation was discontinued if spontaneous circulation was not restored within 10 min.

Autopsy was performed in all animals, and it confirmed that all catheters were in proper position. There was no evidence of cardiac, pulmonary, or thoracic injury.

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Statistical Analysis

Differences in the frequency of mitral valve closure at various levels of compressive force were tested for statistical significance using the χ^2 -test. Mean values of hemodynamic variables and end-tidal CO₂ levels at the three levels of compressive force were evaluated for significant differences by the U-test (Wilcoxon, Mann and Whitney with Bonferroni's correction). The significance level was set at 5%.

Results

Chest compressive forces of 200, 350, and 500 N decreased the anterior-posterior chest diameter by $15.0\% \pm 1.0\%$, $20.0\% \pm 1.3\%$, and $24.8\% \pm 0.5\%$, respectively, of baseline values.

Echocardiographic Findings

Echocardiographic recordings of adequate technical quality were obtained in seven animals. During ventricular fibrillation, mitral valve leaflets showed fibrillatory movements without closure (Figure 2A). At a compressive force of 200 N, 938 CPR cycles were recorded, 700 of which were assessable by echocardiography (Table 1). In 114 (16%) of these, mitral valve closure was observed. At 350 and 500 N. imaging of mitral valve movement became more difficult; thus, fewer CPR cycles (61% and 48%, respectively) were assessable. Mitral valve closure, however, occurred more frequently; it was found in 68% of all cycles evaluated at 350 N (P < 0.001 vs 200N; Figure 2B). A compressive force of 500 N resulted in mitral valve closure in almost all assessable CPR cycles (95%; P < 0.001 vs 200 and 350 N). Individual data, listed in Table 2, reveal considerable differences between the animals, especially at the lowest compressive force. Cycles assessable ranged between 38 and 138, and the percentage of mitral valve closure was 0% in pig 8 and pig 9, but 45% and 50% in pig 6 and pig 3, respectively. At higher compressive forces, both the number of cycles evaluated and the percentage of mitral valve closure were more evenly distributed. At 500 N, 56-80 cycles were available for echocardiographic assessment in each pig, and the rate of mitral valve closure was 100% or close to 100% in all pigs but one. Pigs 3, 5, 6, 7, and 8 were resuscitated successfully; their mitral valve performance and hemodynamic functions did not differ significantly from those of nonsurvivors.

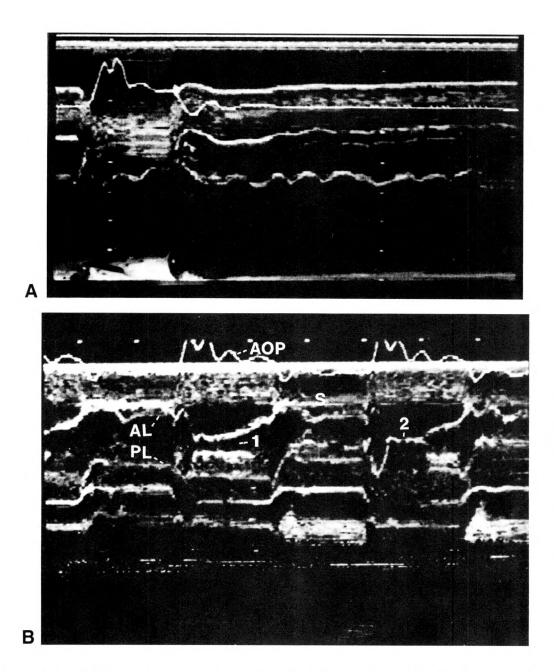
Hemodynamic Findings

Increased compressive force induced significant hemodynamic changes (Table 3). Systolic as well as diastolic aortic pressure increased from 64 and 31 mm Hg to 102 and 44 mm Hg, respectively. Systolic right atrial pressure showed a less marked, although significant, increase from 59 to 87 mm Hg. Common carotid artery flow doubled, and end-tidal CO₂ increased from 0.9% to 1.5% vol/vol. Pulmonary arterial and epidural pressures showed no significant changes. Significant improvements in systolic cerebral (from 28 ± 17 to 63 ± 23 mm Hg; +125%) and diastolic myocardial (from 11 ± 7 to 26 ± 14 mm Hg; +136%) perfusion pressure were observed when compressive force was increased from 200 to 500 N. The systolic pressure gradient between aorta and right atrium averaged 8 ± 7 and 7 ± 7 mm Hg at 200 and 350 N, respectively, but increased to 15 \pm 9 mm Hg with 500 N compression.

Discussion

In the past few years, various authors have employed echocardiography for the assessment of cardiac performance during CPR. Werner et al. (9) and Clements et al. (6) found no mitral valve closure during external CPR in humans; they concluded that the chest pump mechanism was responsible for generating forward blood flow. In contrast, Desmukh et al. (3) reported regular mitral valve function during CPR in pigs, although valve closure diminished after 5 min in nonsurviving animals. They also found that left ventricular chamber area was reduced by 25% during compression systole. A most extensive echocardiography study was performed by Feneley et al. (4) investigating the influence of different manual compression techniques on mitral valve function. They observed direct heart compression and mitral valve closure during brief, high velocity sternal compression (high impulse compression) at compression rates of 60/min or more. The mechanism of mitral valve closure was found to be related to a left ventriculoatrial pressure gradient developing during cardiac compression. Failure of mitral valve closure occurred during prolonged, low velocity compressions (low impulse compression) with compression rates of 40-60/min or less.

These findings are in accordance with the "impulse theory of CPR" (10), which postulates that direct cardiac compression is determined by the compressive momentum, which equals mass of the compression device multiplied by the initial velocity of compression. The force transferred to the chest wall



<u>Figure 2</u>. Echocardiographic M-mode recordings at the mitral valve level during ventricular fibrillation (**A**), and during CPR with and without mitral valve closure (**B**). AOP, aortic pressure tracing; S, interventricular septum; AL, anterior leaflet of the mitral valve; PL, posterior leaflet of the mitral valve; 1, lack of valve closure; 2, mitral valve closure during CPR-systole.

is proportional to the mass of the compression device multiplied by the deceleration as compression proceeds from initial impact to peak compression. The deceleration is determined by the compressive velocity at initial impact. As deceleration approaches zero at peak compression, the total force transferred to the chest equals the mass of the compression device times the initial compressive velocity, which again equals the compression momentum (10,11). Al-

though there is no doubt of the accuracy of these findings, methodologic problems are evident when evaluating the effects of manual CPR. Manual compression techniques are difficult to standardize and thus represent the resultant of variables—mass, velocity, and duration of compression—none of which can actually be held constant in a mathematical sense.

We therefore decided to use a mechanical CPR device to evaluate the influence of compressive force on blood flow mechanism and hemodynamics. This enabled us to hold velocity and duration of compression constant. Proceeding from the generally accepted assumption that the blood flow mechanism is represented by mitral valve function, we focused not

<u>Table 1</u>. Frequency of Mitral Valve Closure During Cardiopulmonary Resuscitation With Various Sternal Compressive Forces (Group Data, n = 7)

Compressive force	Numb CPR o		Mitral clos		
(N)	A	В	n	%	P
200	938	700	114	16	<0.001
350	947	584	399	68	< 0.001
500	1029	494	470	95	< 0.001

CPR, cardiopulmonary resuscitation.

The total number of CPR cycles recorded on video tape is listed in column A, and the number of CPR cycles in which mitral valve function was assessable by echocardiography is listed in column B.

<u>Table 2</u>. Frequency of Mitral Valve Closure During Cardiopulmonary Resuscitation With Various Sternal Compressive Forces (Individual Data)

		200 N compression		350 N compression			500 N compression		
	Cycles		IV sure	Cycles		IV sure	Cycles		AV sure
Pig	(n)	n	%	(n)	п	%	(n)	11	%
3	38	19	50	*****		*******	79	66	84
5	89	27	30	90	79	88	77	73	95
6	123	55	45	88	71	81	80	80	100
7	102	9	8	76	60	79	67	65	97
8	75	0	0	124	74	59	57	57	100
9	135	0	0	104	60	58	78	73	94
10	138	4	3	102	55	54	56	56	100

CPR, cardiopulmonary resuscitation; MV, mitral valve. Only CPR cycles assessable by echocardiography are listed.

only on qualitative but also on quantitative assessment of mitral valve performance. In addition, we decided not to measure left ventricular chamber dimensions, as this would have required removing the probe from the mitral valve level at the cost of continuous monitoring of valve motion. Doppler color flow mapping was not performed, as Feneley et al. (4) have already demonstrated that mitral regurgitation does not occur when mitral valve closure is evident from M-mode imaging. In pilot experiments, the best position of the echocardiography probe proved to be in the anterior mediastinum. By this approach the quality of echocardiography signals was superior to conventional external or transesophageal imaging, as the compression-induced shift of the heart toward or from the probe was minimized. The mediastinal approach was well tolerated; no deterioration of hemodynamic or respiratory parameters was observed. The porcine model was chosen, as the flat-chested shape of porcine thorax—rather than the canine chest geometry—is comparable to that of humans.

Our results clearly indicate that the compressive force applied is a major determinant of the mechanism of blood flow during CPR. At 200 N, blood flow was obvious even in animals lacking mitral valve closure. This confirms the effectiveness of the chest pump mechanism that was proposed by various authors (5-8). With the force increased to 500 N, direct cardiac compression was evident from echocardiography, and almost all CPR cycles showed mitral valve closure. Thus the cardiac pump mechanism appears to be predominant at high compressive force. These results confirm the findings of Deshmukh et al. (3), who observed mitral valve closure during CPR in surviving pigs. They did not report data on compressive force but stated that depth of compression was kept at 25% of the anterior-posterior chest diameter; this is comparable to the sternal displacement found in our study at a compressive force of 500 N. Feneley et al. (4) did not measure compressive force directly but observed regular mitral valve closure with high impulse manual compressions that generated peak aortic pressures of at least 20 mm Hg, which is surprisingly low. Peak aortic pressures with 200 N in our study were three times higher (64 mm Hg), and mitral valve closure was found in 16% of CPR cycles only. This discordance most likely reflects the fact that hemodynamic characteristics of mechanical compressions are different from those of manual techniques (11). Obviously, the fast increase in intracardiac pressures during manual high velocity compression generates a left ventriculoatrial pressure gradient sufficiently high to induce mitral valve closure even at low peak aortic pressures (10). During mechanical compression with a constant rate of 60/ min and a duty cycle of 50%, compressive velocity is lower. Thus, as evident from Feneley et al. (4), a left ventriculoatrial pressure gradient is not expected to occur at low compressive force, which correlates well with the low incidence of mitral valve closure during 200 N compression. However, the increasing incidence of mitral valve closure with 350 and 500 N, respectively, suggests that increasing compressive force compensates for low compressive velocity, resulting in direct cardiac compression and subsequent closure of mitral valve.

The absence of mitral valve closure in human CPR reported by Werner et al. (9) may be due to the following facts. The patients studied had been pronounced brain-dead before the onset of cardiac arrest and had received neither epinephrine nor any other cardiotonic agent. Furthermore, the interval between onset of cardiac arrest and echocardiographic recordings is not stated in the paper; cardiac viability, and thus mitral valve function, might already have dimin-

<u>Table 3</u>. Hemodynamic Findings During Cardiopulmonary Resuscitation With Various Sternal Compressive Forces (mean ± sp.)

	A (200 N)	B (350 N)	C (500 N)	Significance
AP (mm Hg)				
Systolic	64 ± 15	83 ± 18	102 ± 5	AB, AC, BCb
Diastolic	31 ± 6	34 ± 8	44 ± 12	AC ^r
PAP (mm Hg)				
Systolic	60 ± 9	70 ± 16	81 ± 24	NS
Diastolic	18 ± 5	21 ± 6	20 ± 8	NS
RAP (mm Hg)				
Systolic	59 ± 7	80 ± 17	87 ± 10	AB,* AC°
Diastolic	21 ± 9	21 ± 8	17 ± 7	NS
ICP (mm Hg)				
Systolic	33 ± 15	36 ± 15	40 ± 22	NS
Diastolic	10 ± 7	9 ± 7	12 ± 10	NS
QC mean (mL/min)	21 ± 7	36 ± 11	42 ± 5	AC, ^t BC*
ETco2 (% vol/vol)	0.9 ± 0.4	1.3 ± 0.4	1.5 ± 0.2	AC ^a
CPP (mm Hg)				
Systolic	28 ± 17	46 ± 25	63 ± 23	AC"
Diastolic	21 ± 9	26 ± 12	36 ± 14	NS
MPP (mm Hg)				
Systolic	8 ± 7	7 ± 7	15 ± 9	NS
Diastolic	11 ± 7	14 ± 8	26 ± 14	AC*

AP, aortic pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure; ICP, intracranual pressure; QC, carotic flow; ETco₂, end-tidal CO₂; CPP, cerebral perfusion pressure (AP – ICP); MPP, myocardial perfusion pressure (AP – RAP); NS, not significant.

ished before the study. Finally, no changes in ventricular size were observed, which possibly indicates that depth of compression was not sufficient to achieve direct cardiac compression. The report of Clements et al. (6) is more difficult to analyze, as the underlying rhythm during CPR in two patients was not ventricular fibrillation but ventricular and sinus tachycardia, respectively.

As both chest pump and cardiac pump seem to be effective during mechanical CPR, the hemodynamic profiles associated with each of these mechanisms are of major importance. Our results demonstrate that the use of higher compressive force with consecutive mitral valve closure leads to better cerebral perfusion pressures. This was mainly due to the fact that aortic systolic pressure was further increased with the force changed from 350 to 500 N, whereas epidural pressure remained at the previous level. The significant increase in diastolic aortic pressure is probably due to a better filling of the aorta during 500 N systole, which also results in a significantly higher diastolic myocardial perfusion pressure. Furthermore, the significant increases in common carotid artery flow and in end-tidal CO₂ reveal that increasing compressive force enhances cardiac output.

These findings are consistent with those of Deshmukh et al. (3), who observed a systolic pressure

gradient of 16 mm Hg between aorta and right atrium, and also confirm those of Maier et al. (11), who reported a striking difference between intrapleural and aortic pressure during "high impulse CPR" in dogs. In both studies, direct cardiac compression was found to be responsible for generating cardiac output during conventional CPR. Although cardiac output was not measured directly in our study, the relative changes—corresponding to different levels of compressive force—can be estimated from the well-known correlation between cardiac output and end-tidal CO₂ (12,13), i.e., that an increase in end-tidal CO₂ indicates an improvement of lung perfusion.

We therefore conclude that compressive force is a major determinant of the mechanism of blood flow during mechanical CPR. Depending on the force applied, both the chest and the cardiac pump mechanism are effective during CPR. Compressive force may also play an important role in manual CPR with low initial compressive velocity, where the impulse achieved is not likely to generate a left ventriculoatrial pressure gradient. As mitral valve closure is associated with a significant improvement of cerebral and myocardial perfusion pressures, we suggest that CPR techniques should be aimed at achieving direct cardiac compression whenever possible.

n = 7. $^{a}P < 0.05$.

 $^{^{}b}P < 0.005$

P < 0.000.

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Ventilatory Effects of Laparoscopy Under Epidural Anesthesia

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CIOFOLO MJ, CLERGUE F, SEEBACHER J, LEFEBVRE G, VIARS P. Ventilatory effects of laparoscopy under epidural anesthesia. Anesth Analg 1990;70:357–61.

This study evaluates the respiratory effects of laparoscopy under epidural anesthesia in seven female patients (ASA physical status I) scheduled for a gamete intrafallopian transfer procedure. Epidural anesthesia was performed with 15–18 mL of 1.5% plain lidocaine using a catheter inserted at the L3-4 level. The upper level of analgesia to pinprick was measured 20 min after lidocaine injection. Ventilatory measurements and arterial blood gas analyses were performed (a) preoperatively, in the horizontal supine position with a T7-9 level of analgesia; (b) in the 20° Trendelenburg position with a T2-5 level of analgesia; (c) during intraabdominal insufflation of CO₂ through the laparoscope; and (d) after CO₂ exsufflation by manual compression of the abdomen before removal of the laparoscope while in the

horizontal position. On-line measurements of $\dot{V}o_2$, $\dot{V}co_2$, $\dot{V}E$, VT, F, and PET_{CO_2} were made using a Beckman metabolic cart, while the patients breathed room air through an anesthetic face mask. No significant changes in the ventilatory variables were observed in the Trendelenburg position. In contrast, CO_2 insufflation significantly increased $\dot{V}E$ (from 9.1 ± 1.0 L/min to 11.8 ± 2.6 L/min, mean \pm SD), and F (from 16.9 ± 1.9 breaths/min to 23.1 ± 3.3 breaths/min, mean \pm SD), whereas $\dot{V}CO_2$ remained unchanged. Paco₂ remained constant throughout the study. These results suggest that epidural anesthesia may be a safe alternative to general anesthesia for outpatient laparoscopy, as it is not associated with ventilatory depression.

Key Words: SURGERY, LAPAROSCOPY. ANESTHETIC TECHNIQUES, EPIDURAL.

The majority of laparoscopic examinations are performed under general anesthesia. Controlled ventilation is often recommended (1–3), as several factors may induce hypercapnia, including depression of ventilation by anesthetic agents and neuromuscular relaxants, absorption of carbon dioxide (CO₂) from the peritoneal cavity, and mechanical impairment of ventilation by the pneumoperitoneum and the use of a steep Trendelenburg position.

Local anesthesia, in combination with short-acting narcotics used to achieve adequate analgesia, has also been used for laparoscopic surgical procedures in an ambulatory setting (4). This method does not, however, provide optimal surgical conditions. In addition, the use of narcotics may cause undesirable side effects such as nausea, vomiting, and respiratory depression during the postoperative period.

For these reasons, epidural anesthesia has been

suggested to be a suitable alternative method for outpatient laparoscopy (5). The ventilatory changes induced by CO_2 peritoneal insufflation during epidural anesthesia have, as yet, not been clarified. This study was therefore undertaken to investigate the ventilatory effects of laparoscopy performed under epidural anesthesia.

Methods

Patients

Seven female patients (ASA physical status I), mean age 29 yr (range, 23–36 yr), mean weight 55 kg (range, 48–70 kg), undergoing laparoscopy for a gamete intrafallopian transfer procedure, were included in the study, after written informed consent and institutional approval were obtained.

Anesthesia

Lumbar epidural anesthesia was performed in the sitting position with 15–18 mL of 1.5% plain lidocaine. An epidural catheter was inserted at the L3-4

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level for further reinjections. After 10 min, patients were placed in the supine horizontal position, resulting in an upper level of pinprick analgesia between T-7 and T-9.

Ultrasonically guided transvesical follicular aspiration for oocyte retrieval was performed in the lithotomy position. Patients were then placed in a 20° head-down position, and an additional 8–10 mL of 2% lidocaine was injected to obtain a T2-5 level of analgesia.

After insufflation of 2–5 L of $\rm CO_2$ into the abdominal cavity, the gamete intrafallopian transfer procedure was performed by the laparoscopic route. Intraabdominal pressure did not exceed 25 mm Hg during $\rm CO_2$ insufflation.

At the end of the procedure, patients were returned to the horizontal position, and CO₂ was expelled by manual compression of the abdomen before removal of the laparoscope.

Ventilatory Measurements

When the upper level of analgesia ranged between T-7 and T-9, on-line measurements of oxygen uptake (Vo₂ mL/min, STPD), CO₂ output (Vco₂ mL/min, STPD), tidal volume (VT L/breath, BTPS), respiratory rate (F breaths/min), minute-ventilation (VE L/min, BTPS), and end-tidal Pco₂ (PET_{CO₂} mm Hg) were made while the patients breathed room air through an anesthetic face mask.

Arterial pressure and heart rate were continuously monitored using an automatically inflating cuff (Dinamap).

Ventilatory measurements were made using a Beckman Metabolic Measurement Cart (Sensormedics, Fullerton, Calif.) with fast-response sensors (100 ms) for the detection of oxygen and CO₂ partial pressure in expired breath, and with transducers for the measurement of temperature, pressure, and volume. Oxygen was measured with a temperature-controlled polarographic sensor (Beckman OM 11 oxygen analyzer). Carbon dioxide was measured with a dual-beam nondispersive infrared optical system with a pneumatic detector (Beckman LB₂ CO₂ analyzer). A turbine was used for sensing expired air volume, generating pulses as the gas flowed through the transducer. The pulses were counted over time to provide a cumulative volume.

Calibration

The oxygen and CO_2 analyzers, as well as the temperature, pressure, and volume transducers, were calibrated before each study.

Calibration of the gas sensors was automatically accomplished with a zero gas (100% N_2) and a calibration gas (4% CO_2 , 21% O_2 in N_2).

To calibrate the volume transducer, a pump syringe was manually activated to deliver fixed volumes at three different flow rates to the transducer. The microprocessor then performed linearization of the volume. Automatic calibration of the pressure transducer occurred during gas calibration. Oxygen uptake was calculated from the following equation:

$$\dot{V}_{O_2} = \left(F_{I_{O_2}} \times \frac{1 - F_{E_{O_2}} - F_{E_{CO_2}}}{1 - F_{I_{O_2}}} - F_{E_{O_2}} \right) \times \dot{V}_{E_2}$$

where Fr_{o_2} is the inspired oxygen concentration, Fe_{o_2} is the oxygen concentration in the mixed expired gas, Fe_{co_2} is the CO_2 concentration in the mixed expired gas, and \dot{V}_E is the expired minute volume. Carbon dioxide output was measured as $\dot{V}_{CO_2} = \dot{V}_E \times Fe_{Co_2}$.

The accuracy of the Beckman Metabolic Measurement Cart was validated as described by Damask et al. and Wilmore et al. (6,7). Therefore, under the conditions of the study ($FI_{o_2} = 0.21$), we expected an accuracy of $\pm 5\%$.

The study consisted of four observation periods.

The preoperative period (I). Baseline measurements were performed in the supine, horizontal position, at a T7-9 upper level of analgesia, once a steady state had been reached as evidenced by a continuous display of $\dot{V}E$, $\dot{V}O_2$, and $\dot{V}CO_2$.

Period II. After a 20° Trendelenburg tilt, at a T2-5 upper level of analgesia.

Period III. During CO₂ peritoneal insufflation, in the Trendelenburg position.

Period IV. After CO₂ exsufflation by manual compression of the abdomen before removal of the laparoscope, in the horizontal position.

An arterial blood gas analysis was performed at the end of each observation period and 60 min after CO_2 exsufflation. The alveolo-arterial CO_2 difference $[D(A - a)co_2]$ was calculated from simultaneous Per_{CO_2} and $Paco_2$ measurements.

Statistics

All values are expressed as mean \pm sp. Statistical analysis was performed using a two-way analysis of variance and a Newman–Keuls test whenever appropriate. P < 0.05 was considered statistically significant.

<u>Table 1</u>. Changes in Ventilatory Variables (Mean \pm sD)

	I	П	Ш	IV
VE (L/min)	9.15 ± 1.0	10.4 ± 1.7	$11.8 \pm 2.6^{a.b}$	9.9 ± 0.9°
F (breaths/min)	16.9 ± 1.9	18.1 ± 1.9	$23.1 \pm 3.3^{*.d}$	18.7 ± 2.1^{c}
Vr (mL)	548 ± 87	580 ± 88	518 ± 86	536 ± 63
Vo ₂ (mL/min)	285 ± 48	298 ± 36	252 ± 31	257 ± 34
Vco ₂ (mL/min)	231 ± 36	271 ± 58	270 ± 48	243 ± 31
Perco, (mm Hg)	34.9 ± 1.8	34.3 ± 1.4	$31.3 \pm 3.0^{a.d}$	$31.6 \pm 2.0^{\circ}$
Paco ₂ (mm Hg)	38.8 ± 2.3	38.3 ± 1.6	37.5 ± 2.3	37.4 ± 2.8
$D(A - a)CO_2$ (mm Hg)	3.5 ± 1.9	3.7 ± 1.3	$6.4 \pm 2.4^{a.d}$	$5.4 \pm 1.8^{a,b}$
VD/VT (%)	43.1 ± 2.1	41.6 ± 1.2	$47.9 \pm 1.8^{b.e}$	$43.7 \pm 1.5^{\circ}$

I, during epidural anesthesia in the supine, horizontal position; II, after a 20° Trendelenburg tilt; III, during CO₂ insufflation in the Trendelenburg position; and IV, after CO₂ exsufflation in the horizontal position.

Table 2. Demographics

		0 1			
Patient No.	Age (yr)	Weight (kg)	Height (cm)	Duration of Trendelenburg position before CO ₂ insufflation (min)	Duration of CO ₂ insufflation (min)
1	31	50	150	24	8
2	27	52	165	16	8
3	36	48	160	16	6
4	27	52	169	19	15
5	30	61	170	48	10
6	30	54	163	20	15
7	23	70	160	42	14

Results

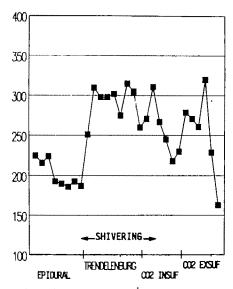
The results of this study are summarized in Tables 1 and 2. The mean duration of CO_2 insufflation was 11 min (range, 6–15 min). At the time of insufflation peak pressure, four of the seven patients complained of shoulder-tip pain.

No changes in mean arterial blood pressure and heart rate were observed during the Trendelenburg tilt or during CO₂ peritoneal insufflation.

The Trendelenburg tilt did not induce any significant change in the ventilatory variables. In four of seven patients, however, shivering after the second injection of lidocaine was associated with a slight increase in oxygen uptake and CO₂ output (Figure 1).

Carbon dioxide insufflation significantly increased minute ventilation and respiratory rate (Figure 2), whereas mean CO₂ output remained unchanged (Figure 3).

 $Paco_2$ remained constant during the entire study, whereas Per_{co_2} decreased significantly during CO_2 insufflation (Figure 4), resulting in an increased alveolo-arterial CO_2 difference $[D(A - a)co_2]$. Pao_2 re-



<u>Figure 1</u>. Carbon dioxide output (Vco₂, mL/min) in patient 5 before, during, and after CO₂ insufflation. Note the increase in Vco₂ during the Trendelenburg tilt resulting from shivering after the second epidural injection of lidocaine.

mained above 90 mm Hg throughout the study in all patients.

One hour after CO₂ exsufflation, Paco₂ was unchanged when compared with baseline values.

Discussion

It has often been suggested that spontaneous ventilation might be hazardous for patients undergoing laparoscopy under general anesthesia (1–3). Marshall et al. (8) demonstrated that spontaneously breathing patients increased arterial Pco_2 by 8.4 ± 3.4 mm Hg (mean \pm sd) during CO_2 peritoneal insufflation. Lewis et al. (9) observed the highest arterial CO_2

p < 0.01 vs L

p < 0.05 vs II.

p < 0.01 vs III.

⁴p < 0.01 vs II.

[°]p < 0.05 vs I. [∫]p < 0.05 vs III.

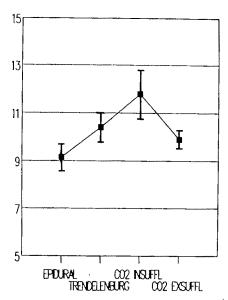


Figure 2. Mean values ± sem of minute ventilation (Ve, L/min) during epidural anesthesia in the horizontal position, during the Trendelenburg tilt, during CO₂ insufflation in the Trendelenburg position, and after CO₂ exsufflation in the horizontal position.

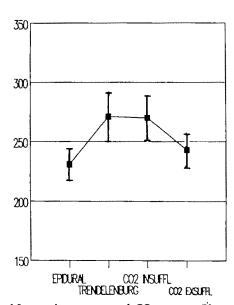


Figure 3. Mean values \pm sem of CO₂ output (VcO₂, mL/min) during epidural anesthesia in the horizontal position, during the Trendelenburg tllt, during CO₂ insufflation in the Trendelenburg position, and after CO₂ exsufflation in the horizontal position.

tension values (above 75 mm Hg) after completion of the surgical procedure, once the intraabdominal pressure had been released. Seed et al. (10) found that patients undergoing laparoscopy during constant volume ventilation had a significant increase in endtidal Pco₂. Furthermore, cardiac dysrhythmias, induced by respiratory acidosis, have been reported during inhalation anesthesia (11,12).

It has generally been accepted that the hypercapnia observed during laparoscopy (1,3,9) is the result

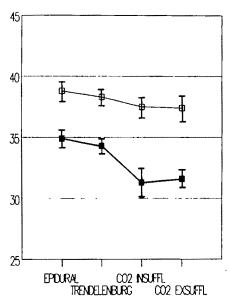


Figure 4. Mean values \pm sem of $Paco_2$ (- \square -, mm Hg) and Per_{co_2} (- \square -, mm. Hg) during epidural anesthesia in the horizontal position, during the Trendelenburg tilt, during CO_2 insufflation in the Trendelenburg position, and after CO_2 exsufflation in the horizontal position.

of peritoneal ${\rm CO}_2$ absorption and mechanical impairment of ventilation caused by the Trendelenburg tilt and the pneumoperitoneum.

In the present study, no significant change in CO₂ output could be demonstrated during laparoscopy, suggesting minimal CO₂ peritoneal absorption. This is in agreement with preliminary findings by De Sousa et al. (13), who showed that the maximal rate of diffusion of CO₂ from the peritoneal cavity was 14 mL/min.

The Trendelenburg position is known to decrease functional residual capacity, total lung volume, and lung compliance (14,15). Pulmonary gas exchange and minute ventilation are, however, not significantly affected by head-down positioning itself in spontaneously breathing patients who are undergoing major gynecologic surgery under combined epidural and light general anesthesia (16).

Brown et al. (4) studied patients undergoing laparoscopy for tubal ligation, using local anesthesia supplemented by small doses of fentanyl. They observed a marked increase in minute ventilation only after establishment of the pneumoperitoneum, whereas arterial Pco₂ remained unchanged.

Our data agree with those of Brown et al. (4). During CO₂ insufflation in the Trendelenburg position, we did not observe any change in Pao₂ and Paco₂. In the face of an unchanged Vco₂, this suggests that alveolar ventilation remained unaltered, despite the increased respiratory work load and ventilation-perfusion inequality, resulting from mechan-

ical compression of the lungs. To maintain an adequate alveolar ventilation, patients had to increase their minute ventilation, suggesting that the mechanisms involved in the respiratory control during CO₂ insufflation remained unaltered. It is possible that patients might have minimized respiratory work by increasing respiratory rate rather than tidal volume.

Several factors may have contributed to increased minute ventilation. First, CO₂ insufflation may have produced an increased number of lung units with high ventilation-perfusion ratios, as demonstrated by a decreased end-tidal Pco2, an increased alveoloarterial CO₂ difference, and an increase in VD/VT ratio. Yet, in spite of this increased respiratory dead space, patients were able to maintain a normal arterial Pco₂, at the expense of an increased ventilation (17). Second, epidurally administered lidocaine has been shown to increase the slope of the ventilatory response to CO₂ (18,19). Finally, persistence of painful stimuli, shivering, abdominal distention, or acid irritation of the peritoneal surface of the diaphragm, innervated from C-4, may have partially changed the peripheral afferent impulses, which led to an increased minute ventilation.

This study suggests that under epidural anesthesia, the mechanisms involved in maintaining an adequate alveolar ventilation during CO₂ insufflation were unaltered. The same ventilatory responsiveness is not likely to occur under inhalation anesthesia (20). Respiratory depression induced by general anesthetics, combined with mechanical impairment of ventilation, may explain the high incidence of hypercapnia observed during laparoscopy under inhalation anesthesia in spontaneously breathing patients (1,3,8,9). As epidural anesthesia does not induce any ventilatory depression, it may be considered as a safe alternative for outpatient laparoscopic surgical procedures.

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Different Effects of Halothane and Enflurane on Diaphragmatic Contractility In Vivo

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KOCHI T, IDE T, ISONO S, MIZUGUCHI T, NISHINO T. Different effects of halothane and enflurane on diaphragmatic contractility in vivo. Anesth Analg 1990;70:362–8.

We examined the effects of halothane and enflurane on diaphragmatic contractility in 12 anesthetized, mechanically ventilated dogs. The diaphragmatic force was assessed from transdiaphragmatic pressure (P_{di}) developed at functional residual capacity against an occluded airway during cervical phrenic nerve stimulation. Animals were randomly assigned to two groups, a halothane group (n = 6) and an enflurane group (n = 6). The P_{di} stimulus-frequency relationship was compared at anesthetic levels of 1, 1.5, and 2 MAC (minimum alveolar concentration) in each group. The sequence of changing anesthetic concentration was randomized. In addition, the P_{di}-frequency relationship was also compared between 1 MAC of halothane and enflurane in 8 of 12 dogs. In animals anesthetized with enflurane, P_{di} significantly decreased with 50- and 100-Hz stimulation in the presence of increasing MAC values, whereas P_{di} at

10-Hz stimulation was not affected by the depth of anesthesia. P_{di} with 20-Hz stimulation during 2 MAC enflurane also decreased significantly below P_{di} levels seen at 1 and 1.5 MAC. By contrast, with halothane there was no difference in P_{di} at any of the stimulation frequencies during any of the three levels of anesthesia. There was no statistical difference, however, between P_{di}-frequency relationships during 1 MAC of halothane and enflurane in eight animals. From these results, we conclude that halothane does not impair diaphragmatic contractility any more than enflurane does, but enflurane decreases force generation of the diaphragm at high stimulation frequencies in a dose-related fashion. This depressant effect of enflurane occurs mainly through the impairment of neuromuscular transmission and/or membrane excitability. Part of its effect is probably related, however, to the impairment of excitation-contraction coupling, as suggested by the depression of P_{di} at 2 MAC in response to 20-Hz stimulation.

Key Words: ANESTHETICS, volatile—halothane, enflurane. MUSCLE, skeletal—diaphragm.

It is well recognized that volatile anesthetics depress skeletal muscle contractility in vitro (1,2). This depression could be accounted for by the effects of the anesthetics on the neuromuscular transmission and/or contractile machinery within the myocyte. Indeed, Waud and Waud have demonstrated that halothane and enflurane depress not only indirect twitch response at 3.5–5 MAC and 1.5–2.5 MAC, but also the direct response at 8–10 MAC and 6–8 MAC, respectively (1).

Recently, Aubier et al. have developed a method to assess the contractility of the diaphragm in vivo and have examined the effects of various pharmacologic agents on the fatigued diaphragm (3–6). In this

connection, Dureuil et al. (7) and Veber et al. (8) have demonstrated that halothane and isoflurane impair contractile properties of the diaphragm in vivo in rats. Furthermore, Clergue et al. (9) also demonstrated that halothane impairs contractile properties of the diaphragm in spontaneously breathing dogs. However, results obtained under such experimental conditions may not be applicable to mechanically ventilated dogs, as hypercapnia and acidosis depress diaphragmatic contractility by themselves (10). In addition, data are not available regarding the effects of enflurane on the canine diaphragm. Accordingly, we examined the effects of halothane and enflurane on diaphragmatic function in intact dogs.

Materials and Methods

Animals

Institutional approval for the study was obtained from the Animal Care and Use Committee of Chiba

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University School of Medicine. Twelve mongrel dogs weighing 10-15 kg were anesthetized intravenously in the supine position with 15 mg/kg thiopental, and anesthesia was then maintained with either halothane (n = 6) or enflurane (n = 6) (1–1.5 MAC in oxygen). Initially, oral cuffed endotracheal tubes were inserted; subsequently, tracheal cannulae were placed through tracheotomies and mechanical ventilation was started. The femoral artery was cannulated to monitor blood pressure and to draw blood samples for measurement of arterial blood gas tensions using the IL blood gas analyzer (Instrumentation Laboratories, model 1302). The femoral vein was also cannulated for the administration of fluids and bicarbonate to correct acidosis. Rectal temperature was continuously monitored by a thermistor and was maintained at 37°-38°C throughout the experiments by heating lamp. Airflow (V) was measured by a pneumotachograph (Nihon Koden TV-122T) and a differential pressure transducer (Nihon Koden TP-602T) at the connection between the three-way stopcock and the connector to the tracheal cannula. Changes in lung volume (ΔV) were measured by an electrical integration of the V signal. End-tidal concentrations of anesthetics were continuously monitored by an anesthetic gas analyzer (Datex Normac). The experimental design is schematically illustrated in Figure 1.

Transdiaphragmatic Pressure

A catheter with a thin-walled latex balloon (5 cm length, 1.0 mL air) positioned in the abdominal cavity beneath the costal part of the diaphragm through a small midline abdominal incision was connected to one side of the differential pressure transducer (Nihon Koden TP-601T). The surgical incision was then closed tightly in layers. Another catheter with a latex balloon (0.4 mL air) was also positioned in the middle third of the esophagus, and was connected to the other side of the transducer. Thus, transdiaphragmatic pressure (Pdi) was determined as the difference between the pressures recorded by the two ballooncatheter systems. During a given study period, Pdi (cm H₂O) was recorded during electrical stimulation of the phrenic nerve at different frequencies while the airway was occluded at end-expiratory lung volume by turning the three-way stopcock. Constancy of diaphragm geometry and muscle length during contraction was achieved by placing a closely fitted plaster cast around the abdomen and lower one-third of the rib cage.

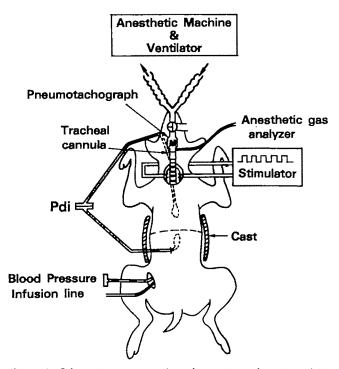


Figure 1. Schematic representation of experimental settings. Animals were placed in the supine position and mechanically ventilated with respiratory volumes measured by a pneumotachograph. Transdiaphragmatic pressures (P_{di}) were measured using two balloons as the difference between abdominal and esophageal pressures. Cervical phrenic nerves were bilaterally stimulated with an electric stimulator. Catheters were inserted in the femoral artery and vein to monitor arterial blood pressure and to infuse fluids.

Phrenic Nerve Stimulation

The phrenic nerves were identified bilaterally in the lower necks, and isolated from the surrounding tissue. A stimulating electrode was positioned on each, and the nerves were stimulated using an electric stimulator (Nihon Koden SEN-3201) that delivered trains of supramaximal equidistant square-wave pulses. Supramaximal stimulation was determined by recording diaphragmatic twitches as the stimulation voltage was increased. Maximal response was determined by measuring twitch amplitude, and maximal stimulation was achieved at approximately 25 V. The voltage was then increased 10%-20% to ensure that stimulation remained supramaximal. Pulse duration was set to 0.2 ms. Stimulation trains were applied for 2–3 s at increasing frequencies of 10, 20, 50, and 100 Hz. Two stimulations were made at each frequency at 2-min intervals, and the average value of the two was used in the data analysis.

Experimental Protocol

Diaphragmatic contractility was assessed during three levels of anesthesia in each animal, namely 1,

Table 1. Average ± SEM Values of Mean Blood Pressure (MBP), Hydrogen Ion Concentration ([H⁺]), Paco₂, and Pao₂ at Three Levels of Halothane and Enflurane Anesthesia

	MBP (mm Hg)	[H ⁺] (nmol/L)	Paco ₂ (mm Hg)	Pao ₂ (mm Hg)
-	(Hill Fig)	(Inflore)	(11111 11g)	(11111 118)
Halothane group				
1 MAC	110.0 ± 10.0	41.8 ± 1.1	33.8 ± 1.5	460.7 ± 24.5
1.5 MAC	$90.7 \pm 8.5^{\circ}$	41.7 ± 1.0	36.6 ± 1.6	458.1 ± 14.1
2 MAC	$75.5 \pm 7.3^{b,c}$	41.5 ± 0.8	34.5 ± 0.8	457.2 ± 28.3
Enflurane group				
1 MAC	109.7 ± 9.1	41.7 ± 1.1	37.6 ± 0.9	508.8 ± 8.2
1.5 MAC	$90.0 \pm 9.6^{\circ}$	39.7 ± 1.4	35.6 ± 1.6	460.3 ± 8.2
2 MAC	$63.5 \pm 8.3^{b,d}$	40.4 ± 1.5	35.5 ± 1.6	458.5 ± 21.0

 $^{^{\}bullet}P < 0.05 \text{ vs } 1 \text{ MAC}.$

1.5, and 2 MAC of either halothane or enflurane, each after 1 h of steady state conditions. The sequence of changing anesthetic level was randomized between animals. In addition, in 8 of 12 dogs the relationship between P_{di} and frequency of stimulation was assessed during 1 MAC of halothane and enflurane at the end of the first protocol. This was done by changing anesthetic either from halothane to enflurane (n = 4) or from enflurane to halothane (n = 4).

Arterial blood gas tensions and mean blood pressure were measured at each depth of anesthesia at the end of the run. Arterial blood pressure, P_{di} , \dot{V} , and ΔV were recorded on a four-channel recorder (Nihon Koden Recticorder). All values are given as mean \pm sem. Statistical analysis was performed using two-way analysis of variance and the Tukey test.

Results

Table 1 illustrates the average \pm sem values of mean arterial blood pressure, hydrogen ion concentration ([H⁺]), Paco₂, and Pao₂ in two groups under each experimental condition. Blood pressure decreased significantly with increasing depth of anesthesia in both groups; [H⁺] and blood gas tensions remained essentially constant regardless of the level of anesthesia.

Representative recordings of $P_{\rm di}$ obtained in a halothane-anesthetized animal during phrenic nerve stimulation of various frequencies are shown in Figure 2. As illustrated in Figure 2A, $P_{\rm di}$ increased with increasing stimulation frequencies from 10 to 100 Hz. Figures 2B and 2C correspond to the tracings obtained at 1.5 and 2 MAC of halothane, respectively. It can be seen from these figures that, with a given frequency of stimulation, $P_{\rm di}$ is essentially constant regardless of the level of anesthesia.

Figure 3 shows similar tracings obtained in an enflurane-anesthetized dog. In contrast to Figure 2, P_{di} with 50 and 100 Hz during 1.5 and 2 MAC showed an initial rapid increase followed by a gradual decline in pressure during phrenic nerve stimulation. Although duration of stimulation longer than 3 s may produce plateau pressure of P_{di} , it may also induce muscle fatigue, and so we limited the duration of stimulation to 2–3 s, with measurement of P_{di} being made 2 s after starting the stimulation.

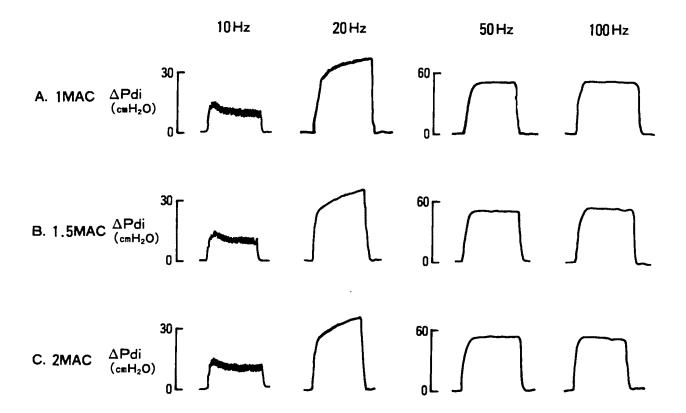
Table 2 demonstrates the mean \pm sem values of P_{di} at stimulation frequencies of 10, 20, 50, and 100 Hz under three levels of anesthesia in both groups. There were no statistical differences among the values of P_{di} at each stimulation frequency under the three depths of anesthesia in the halothane group. By contrast, enflurane-anesthetized animals developed significant decreases in P_{di} at 50- and 100-Hz stimulations with increasing depth of anesthesia. Although statistically insignificant, P_{di} with 20 Hz at 1.5 MAC enflurane was slightly greater than that of 1 MAC, which is similar to the observation made by Veber et al. in isoflurane-anesthetized rats (8). By contrast, P_{di} of 2 MAC enflurane was significantly decreased from the value of 1.5 MAC at this stimulation frequency.

Figures 4 and 5 depict the force-frequency relationships in the halothane (Figure 4) and enflurane (Figure 5) groups. Values of P_{di} were expressed as the percentage of the maximum P_{di} obtained in each animal. It is apparent from Figure 5 that enflurane exerts a dose-dependent decrease of diaphragmatic force generation at higher stimulation frequencies of 50 and 100 Hz. Enflurane at 2 MAC also decreased tension development at 20-Hz stimulation more than it did at 1 and 1.5 MAC. By contrast, halothane did not affect force-generating properties at any stimulation frequencies. Figure 6 illustrates the force-

 $^{^{}b}P < 0.01 \text{ vs } 1 \text{ MAC}.$

[°]P < 0.05 vs 1.5 MAC.

 $[^]dP < 0.01 \text{ vs } 1.5 \text{ MAC}.$



frequency relations of 1 MAC of halothane and enflurane anesthesia in eight animals. Although $P_{\rm dt}$ of enflurane tended to be less than that of halothane at the range of frequencies between 20 and 100 Hz, the difference was not statistically significant.

Discussion

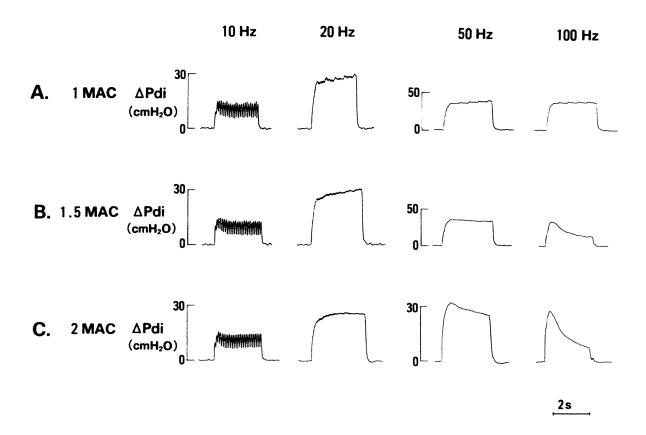
The main findings of this study are (a) enflurane, at 1.5 and 2 MAC levels, decreases contractility of the diaphragm at higher stimulation frequencies of 50 and 100 Hz more than it does at 1 MAC, whereas enflurane does not change the contractility with 10-Hz stimulation; and (b) halothane, in contrast, does not affect diaphragmatic contractile properties, at least not in the anesthetic depths used in the present experiment. This implies that the effects of halothane and enflurane on diaphragmatic function differ and that the depressant effect of enflurane is MAC-dependent.

The contractile properties of the diaphragm were assessed by its force-frequency characteristics. This method has been extensively used for skeletal muscle (11), and recently in humans and dogs (4–6,9) for the diaphragm. In the latter, force generated by the diaphragm for a given electrical stimulation was measured in terms of $P_{\rm di}$. As previously demonstrated, the pressure generated by the diaphragm for

<u>Figure 2</u>. Transdiaphragmatic pressures (P_{ti}) in a halothane-anesthetized animal at stimulating frequencies of 10, 20, 50, and 100 Hz during 1, 1.5, and 2 MAC levels of anesthesia.

a given stimulation is affected by its length and geometry (12,13). A major determinant of the length and geometry of the diaphragm is lung volume. Conceivably, therefore, the change in P_{di} observed during experimental procedures might be secondary to changes in the end-expiratory lung volume of the animals. However, this is not the case in the present experiments, as the lung volume at which the measurements were made was the functional residual capacity and its constancy was monitored by measuring the end-expiratory transpulmonary pressure. Hence, changes in lung volume during the experimental procedures can be reasonably excluded. Furthermore, by placing a cast around the lower third of the thorax and abdomen, we avoided the deformation of the thoracoabdominal structures.

Moreover, P_{di} generated during diaphragmatic stimulation does not depend only on diaphragmatic strength but also on abdominal wall compliance. In this regard, both halothane and enflurane may increase abdominal compliance by relaxing the abdominal muscles, which in turn, could have influenced P_{di}. This would decrease P_{di} at a given rate of phrenic stimulation even in the absence of the impairment of diaphragmatic contractility. However, this effect is



<u>Figure 3</u>. Experimental records of $P_{\rm di}$ obtained in an enflurane-anesthetized dog at stimulating frequencies of 10, 20, 50, and 100 Hz during 1, 1.5, and 2 MAC levels of anesthesia.

unlikely in our model, as the abdominal cast ensured a constant abdominal displacement during stimulation. In this connection it should be noted that, in the dog with the cast in place, shortening of diaphragmatic length was <10% at any frequency of stimulation and thus did not affect the tension produced for a given stimulus (13).

It has been suggested that selective loss of force at low frequency stimulation is closely related to the impairment of excitation-contraction coupling (14), whereas selective loss of force at high frequency stimulation indicates failure of neuromuscular transmission and/or impaired membrane excitation (11,15). Therefore, the reduction of Pdi in response to 50- and 100-Hz stimulation at 1.5 and 2 MAC enflurane is presumably due to the impairment of neuromuscular transmission and/or membrane excitation. Similarly, the decrease of Pdi at 20-Hz stimulation during 2 MAC enflurane could be due to a failure of excitation-contraction coupling. This alteration of diaphragmatic contractility may be related to a decrease in energy substrate supply. Indeed, the ability of diaphragm to receive metabolic substrates in amounts adequate to sustain contraction depends on

the diaphragmatic blood flow (16). The dosedependent depression of contractile strength by enflurane might be due to the decrease of arterial blood pressure, with which diaphragmatic blood flow is closely related. However, this reasoning may not be applied to 1.5 MAC of enflurane because the mean arterial blood pressure was not different between the 1.5 MAC halothane and the 1.5 MAC enflurane, and because blood flow to the diaphragm should be autoregulated at blood pressures above 70 mm Hg as shown by Hussain et al. (17). Alternatively, the alteration of cardiac output as well as the ability of the diaphragm to autoregulate its blood flow may have contributed to the different effects of halothane and enflurane on the diaphragmatic contractility. To elucidate the underlying mechanisms responsible for the impairment of diaphragmatic contractility by enflurane, further studies—including measurements of electromyographic activity of the diaphragm, diaphragmatic blood flow, and the energy balance of the diaphragm (16,17)—would be needed.

Our finding of decreased force-generating properties of enflurane at higher frequencies of stimulation is compatible with the observation made by Veber et al., showing depression of $P_{\rm di}$ at 50 and 100 Hz by isoflurane in rats (8). On the other hand, our results are somewhat different from those reported by others for halothane (7,9). Dureuil et al. (7), for example,

Table 2. Values of Transdiaphragmatic Pressure at Various Stimulation Frequencies of the Phrenic Nerve at Three Levels of Halothane and Enflurane Anesthesia

	P _{di} (cm H ₂ O)					
	10 Hz	20 Hz	50 Hz	100 Hz		
Halothane group						
1 MAC	18.8 ± 5.2	35.9 ± 5.8	44.8 ± 6.1	45.4 ± 6.1		
1.5 MAC	18.8 ± 4.5	37.5 ± 4.6	44.3 ± 5.0	44.4 ± 5.1		
2 MAC	18.4 ± 4.2	37.0 ± 5.2	44.9 ± 6.7	44.9 ± 6.8		
Enflurane group						
1 MAC	12.5 ± 2.5	27.3 ± 3.0	37.4 ± 4.7	34.0 ± 4.4		
1.5 MAC	12.7 ± 2.5	28.6 ± 3.0	32.7 ± 3.3	$21.0 \pm 5.0^{\circ}$		
2 MAC	11.0 ± 2.1	22.8 ± 3.3^b	$25.3 \pm 4.1^{a,b}$	$14.1 \pm 3.8^{a,b}$		

 $P_{\rm div}$ transdiaphragmatic pressure. P < 0.01 vs 1 MAC.

^bP < 0.05 vs 1.5 MAC.

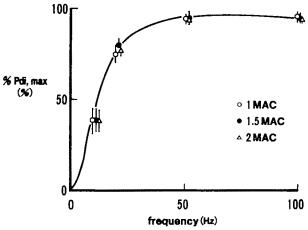


Figure 4. Force-frequency response curves of the diaphragm at three levels of halothane anesthesia (n = 6 dogs). Values of P_{dl} are expressed as the percentage of the maximum Pdi determined in each animal during the experimental procedures. Each point represents average data (± sem). There was no statistically significant difference among the three levels of anesthesia at any stimulation frequencies.

demonstrated in rats that 0.5-1.5 MAC of halothane produces a marked decrease in diaphragmatic contractility at stimulation frequencies ranging from 0.5 to 100 Hz, whereas halothane was without effect on hindlimb muscle. Also, Clergue et al. (9) demonstrated that halothane depresses both Pdi and electromyographic activities of the canine diaphragm at all stimulation frequencies (10-100 Hz). Both these results suggest that the reduction of contractility of the diaphragm by halothane is caused principally by impairment of the excitation-contraction coupling process. The difference between our results with halothane and those of Dureuil et al. and Clergue et al. with halothane may be explained by the difference of the species and/or the differing experimental conditions. In this connection, as the study by Clergue et

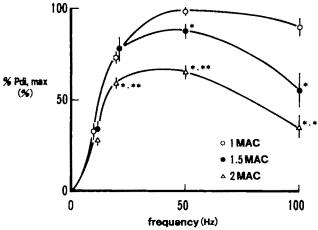
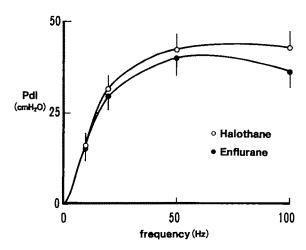


Figure 5. Force-frequency response curves of the diaphragm at three levels of enflurane anesthesia (n = 6 dogs). Transdiaphragmatic pressure at 50 and 100 Hz was significantly different among the three levels of anesthesia. Transdiaphragmatic pressure at 20 Hz during 2 MAC was also significantly less than it was during 1 and 1.5 MAC. * and ** represent statistical difference (*P < 0.01 vs 1 MAC; **P < 0.01 vs 1.5 MAC). For definitions see legend to Figure 4.

al. was conducted in spontaneously breathing animals, hypercapnia and acidemia that may have developed with increasing halothane concentrations could have impaired diaphragmatic contractility (10).

Our results suggest that the impairment of the diaphragmatic contractility associated with enflurane and, hence, the ventilatory pump dysfunction may be—at least in part—responsible for ventilatory depressant effects greater with enflurane than with halothane. The clinical importance of this phenomenon remains to be demonstrated in humans.

We conclude that increasing enflurane concentrations produce progressive decreases in the force generation of the canine diaphragm in response to higher frequencies of stimulation. By contrast, increasing halothane concentrations do not affect dia-



<u>Figure 6</u>. Force-frequency relationship at 1 MAC of halothane and enflurane anesthesia obtained in eight dogs. Although at any given frequency average values of P_{dl} for halothane anesthesia were greater than those obtained for enflurane anesthesia, the difference was not statistically significant.

phragmatic contractile properties, at least in the range of MAC multiples used in the present experiments. Clearly further studies are needed to elucidate the mechanisms underlying the differing effects of various volatile anesthetics on diaphragmatic function in vivo.

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Progressive Changes in Electroencephalographic Responses to Nitrous Oxide in Humans: A Possible Acute Drug Tolerance

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AVRAMOV MN, SHINGU K, MORI K. Progressive changes in electroencephalographic responses to nitrous oxide in humans: a possible acute drug tolerance. Anesth Analg 1990;70:369–74.

The possibility of acute tolerance to nitrous oxide was examined during halothane anesthesia in humans. Nitrous oxide was added to the inspired gas twice. The first admixture induced three successive stages of electroencephalogram (EEG): δ -waves lasting for 13 ± 12 min, θ -waves lasting for 41 ± 21 min, and, finally, spindle-type waves. The spindle-type EEG was similar to that of halothane anesthesia in configuration, but smaller in amplitude and faster in frequency than that seen during halothane anesthesia. The second admixture, given after a 20-30-min

interval, induced a continuous &-wave EEG in one patient, θ -waves followed by spindle EEG in eight patients, and spindle-type EEG in four patients. The successive changes of electroencephalographic response during the first admixture indicate that an alteration of central nervous system function occurred. The altered state was maintained in the absence of nitrous oxide: responses to a second admixture were characteristic of the later, altered, stages of responses seen after the first admixture. These findings support the view of acute tolerance to nitrous oxide.

Key Words: ANESTHETICS, GASES—nitrous oxide. TOLERANCE, NITROUS OXIDE. BRAIN, ELECTROENCEPHALOGRAPHY—nitrous oxide.

Progressive diminution in incidence and, ultimately, disappearance of nitrous oxide (N2O)-induced electroencephalographic slow waves during continuous administration of N2O in cats was first documented by one of the present authors (1). This observation was followed by several reports of similar alterations of N₂O actions including analgesia, in both humans and rats (2-4), depression of righting reflex (5), anticonvulsive action (6,7), depression of somatosensory evoked responses, and excitation of the brainstem reticular neurons (7). All these reports claimed to represent development of acute drug tolerance. Drug tolerance, i.e., "progressive diminution of susceptibility to the effects of a drug, resulting from its continued administration" (8), is an expression of an acquired function of the organism resulting in reduction of drug action. The alteration of function requires structural alterations of cellular constituents, such as receptor proteins, ion channels, and drug-metabolizing enzymes. It takes time for such structural alter-

ations to be established. Once established, however, these changes persist for a certain period of time even after withdrawal of the drug, and the altered function is maintained as well. All previous studies claiming development of tolerance to N2O were not conclusive, as they dealt only with the phase of diminution of the susceptibility of the central nervous system (CNS) to the drug, and not with the phase of maintenance of diminished susceptibility after withdrawal of the drug. As electroencephalographic oscillation is hypothesized to be a summation of postsynaptic potentials of the apical dendrite of pyramidal neurons, the changes of electroencephalographic pattern, however it may be processed, do not give information about how actively the cortical cells are firing (for further detail see Reference 9). This indicates that the changes in electroencephalographic pattern do not give information about whether the action of a given drug is diminished or increased. However, if a change in the electroencephalographic pattern occurs during a steady state administration, it certainly indicates that some change is occurring in the responsiveness of the brain. Using the electroencephalographic responses to N₂O in humans, the present study attempts to confirm, first, whether any alteration occurs in the brain function during a con-

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tinuous administration of N_2O , and, second, whether the altered function of the brain, if it occurs, is maintained for a certain period of time after withdrawal. As the protocol of the study included a period of withdrawal of N_2O during surgery, it was administered with a background of halothane-oxygen anesthesia.

Materials and Methods

Fifteen ASA physical status I and II patients-14 women and one man, aged 38.8 ± 10 yr (mean \pm sp)—who were scheduled for elective lower abdominal gynecologic (n = 12) or plastic (n = 3) surgery gave written informed consent for the study, which was approved by the institutional Human Investigation Committee. All patients were free from neurological disorders, and no patient was being treated with any chronic medication. No premedication was given. Anesthesia was induced with 3% halothane in oxygen, the trachea was intubated with the aid of pancuronium, 6 mg intravenous, and the lungs were ventilated automatically at a constant ventilation volume. Concentrations of respiratory and anesthetic gases were measured continuously with a mass spectrometer (Parkin-Elmer Medical Gas Analyser 1100). The end-expiratory concentration of halothane was maintained at 0.75-1.0 MAC and that of CO₂ at 30-35 mm Hg. Body temperature was monitored with a rectal thermometer probe and maintained at $36 \pm 1^{\circ}$ C with a heating water mattress.

Nitrous oxide was added to the anesthetic gas mixture, at an inspiratory concentration of 65%, twice during the anesthesia. The first exposure to N_2O began 30–40 min after intubation and 10–15 min after the start of surgery, when a stable electroencephalographic pattern of halothane-oxygen anesthesia was confirmed. The first exposure lasted for 96 \pm 15 min, and was then discontinued for a period of 20–30 min, during which the electroencephalographic pattern of halothane-oxygen anesthesia was completely reestablished. This was followed by a second exposure to N_2O of the same concentration, which was limited by the end of surgery and lasted for 25 \pm 8 min.

The electroencephalogram (EEG) was continuously monitored (San Ei 1A91) from scalp electrodes filled with conductive paste and placed bilaterally at frontal, parietal, and occipital positions with reference electrodes at the ear lobes. The electrode impedance measured at the beginning and the end of study was always less than 15 k Ω . The EEG was simultaneously recorded on a magnetic tape (Teak MR30) for a subsequent off-line power spectrum analysis by

Fast Fourier Transformation with a signal processor (San Ei7T18).

Results

Data were collected from 15 patients, but those from two patients were discarded due to unstable recording conditions and excessive noise contamination.

In all 13 patients, halothane induced electroencephalographic activities of 10–16 Hz, 50–80 μ V with a typical spindling pattern. The addition of N₂O induced three electroencephalographic stages, distinguishable by visual inspection: the first stage, that of δ -wave activity, was followed by a second stage of θ -wave activity, and finally by a third stage of 17–22-Hz spindle-type activity (Figures 1 and 2).

The first stage of continuous δ -wave (1–2 Hz), high-amplitude (100–200 μ V) EEG appeared at 3 \pm 0.8 min in 12 patients out of 13 (Figure 3). This electroencephalographic stage continued for 13 \pm 12 min in 11 patients, and for 90 min of the whole period of addition of N₂O in one patient (patient 12). One patient (patient 13) maintained the control EEG of halothane-oxygen anesthesia and did not show any response to N₂O on the EEG.

The second stage of θ -wave (4–5 Hz) EEG of moderate amplitude (50–80 μ V) appeared at 17 \pm 12 min after the start of addition of N₂O, when the high-amplitude slow waves of the first stage started to appear intermittently. This pattern dominated the EEG during the next 41 \pm 21 min in eight patients (patients 1–8). Three patients (patients 9–11) maintained this electroencephalographic stage during the whole period of administration of N₂O.

The third stage of EEG appeared after 53 \pm 22 min of adding N₂O in eight patients (patients 1–8), and was similar to the EEG of halothane-oxygen anesthesia, except for the lower amplitude (25–50 μ V) and faster frequency (17–22 Hz). When N₂O was withdrawn, the EEG increased in amplitude and decreased in frequency in all patients, and within 10 min it returned virtually to the pattern of the control, pre-N₂O period. Nitrous oxide was eliminated rapidly, and after 20 min its end-tidal concentration was below 3%.

Changes in the EEG during the second administration of N_2O did not follow the pattern seen with the first exposure. The first electroencephalographic stage of high-amplitude δ -waves was bypassed and the second electroencephalographic stage appeared in eight cases (patients 1, 5–11) and was rapidly transformed to the third-stage EEG in four of them (patients 1, 6, 8, 9): in three cases the third-stage EEG appeared immediately (patients 2–4).

First N2O exposure

stage II stage III s

Both during the second and the third stages of the first and the second exposures, sudden reappearance of bursts of δ -waves of the first-stage EEG was noted in six patients (patients 1, 3, 4, 7, 8, 10): these bursts are marked with arrows in Figure 3. They were associated with coughing (n = 3) and with a sudden intense stimulation such as traction of the uterus (n = 4), omentum (n = 2), and peritoneum (n = 2). This sudden electroencephalographic response was transitory, and the second- or third-stage electroencephalographic patterns resumed rapidly, probably due to cessation of the stimulation (Figure 4).

Discussion

The present study confirmed that during background halothane anesthesia, the human electroencephalographic response to continuous administration of N_2O changes with time: δ -waves (stage 1) appeared immediately after addition of N2O, followed by θ-waves (stage 2), and, finally, an electroencephalographic pattern similar to that of halothane-oxygen anesthesia (stage 3) was reestablished. The thirdstage EEG had a similar configuration to that of halothane-oxygen anesthesia except that the amplitude was smaller and the frequency was greater. After a 30-min interval, a second administration of N₂O did not repeat the same sequence of electroencephalographic changes; instead, stage 1 or both stages 1 and 2 were bypassed, and stages 2 or 3 appeared immediately.

Second N₂O exposure

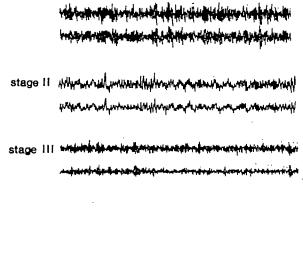


Figure 1. Electroencephalographic responses to the addition of 65% N_2O to 1.0 MAC halothane-oxygen anesthesia in a 30-yr-old woman undergoing ovarian cystectomy (patient 3). LF, left frontal lead; RF, right frontal lead; stage 1, stage of δ -wave EEG; stage 2, stage of θ -wave EEG; stage 3, stage of spindle-wave EEG. For details, see text.

The addition of N_2O to halothane affects the efficiency of the halothane vaporizer (10) and induces a second gas effect (11) and end-tidal CO_2 elevation (12,13). These were all of minor magnitude and did not account for the observed electroencephalographic slowing, as the second exposure did not induce the same sequence of electroencephalographic responses. The electroencephalographic changes are, therefore, related to the response of the CNS to N_2O .

It is generally agreed that the slower the electroencephalographic frequency, the greater the suppression of CNS activity by anesthetics (14). The addition of N₂O to halothane does supplement the anesthetic state with regard to behavioral criteria, e.g., MAC (15). Nevertheless, neurophysiologic studies have indicated that the CNS actions of N₂O are a mixture of CNS stimulation and depression: the CNS stimulation is observed in the activation of reticular cell firing (7,16,17) and sympathetic preganglionic activity (13,18), and the CNS depression in the suppression of the auditory (16) and somatosensory (7) evoked responses, the nociceptive neural response in the spinal cord (19,20), and enflurane-induced convulsion (7). Similar slow-wave EEGs of θ - δ bands are produced by a group of anesthetics, such as diethyl

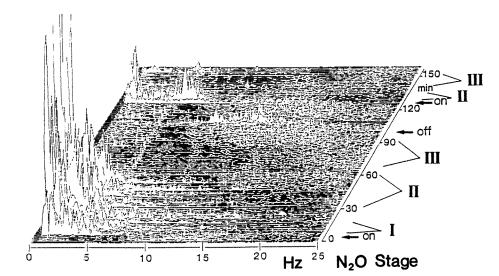


Figure 2. Electroencephalographic power spectrum array showing the response to addition of N2O. Abscissa represents frequency of EEG activities in hertz (epoch length, 64 s), ordinate the power of EEG in square microvolts, and time axis the time-course of addition of N₂O. Roman numbers I-III represent the electroencephalographic stages. Nitrous oxide increased the power in the lower frequency bands, but this effect decreased gradually with time. The total power after the second N2O administration was smaller than that after the first exposure, and the attenuation of power was faster.

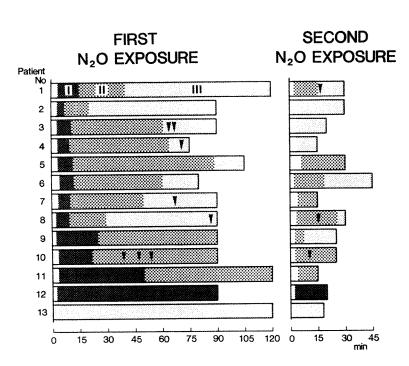
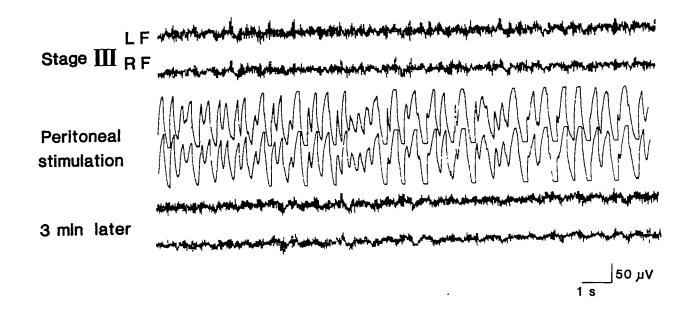


Figure 3. Time-course of the transition of electroencephalographic stages in 13 individual patients. *Arrows* indicate the sudden reappearance of δ -wave activity (see also Figure 4). The patient numbers in this figure correspond to those appearing in the text.

ether (16,21), cyclopropane (22,23), and ketamine (24,25) both in cats and humans; all of these drugs induce activation of brainstem reticular-cell firing in cats (1). The slow waves induced by these anesthetics are exaggerated by high-frequency electric stimulation of the skin in cats, which is associated with an enhancement of the reticular-cell firing (26). Surgical noxious stimulation and intravenous administration of depolarizing muscle relaxants, which produce arousal stimulation, induce similar electroencephalographic slow waves in human infants and children anesthetized with halothane and oxygen (27,28). Kaada et al. (29) and Prince and Shanzer (30) reported that, in cats, high-frequency electric stimulation of

the brainstem reticular core, inducing low-voltage fast-wave EEG in an unanesthetized state, produced θ - and δ -wave EEG at a certain level of pentobarbital and ether anesthesia. In the present study, although not directly verified, coughing or intense surgical stimulation were possible factors contributing to the reappearance of the δ -wave EEG, which had disappeared during stages 2 and 3. All these findings combined together indicate that the δ - θ band slowwave EEG observed during stages 1 and 2 were induced by the CNS-stimulating action of N₂O.

When a reversible change occurs in the response to a drug during its continuous administration, the underlying mechanism is either tolerance or sensitiza-



tion. As EEG alone does not give information on how much CNS activity may be suppressed or excited, the observed electroencephalographic changes alone in the present study do not give information about whether the mechanism represented tolerance or sensitization. Previous studies have shown that various CNS actions of N₂O—such as activation of the reticular cell firing (7), and suppression of the amplitude of somatosensory evoked response (7) and the convulsant property of enflurane—diminished with time. These observations support the view that the changes of the electroencephalographic pattern in the present study reflected a diminution of the CNS-stimulating action of N₂O, i.e., tolerance, not sensitization. Further, the absence of first-stage or of first- and secondstage EEG during the second exposure to N₂O indicated that the altered brain function during the first exposure was retained during the withdrawal period, which also supports the possibility of drug tolerance. The tolerance observed in the present study was, however, partial, because the return of the halothaneoxygen pattern was never completely achieved during the phase of diminution of drug susceptibility.

Noxious stimulations reproduced stage-1 EEG during stages 2 and 3 in the present study, and noxious stimulation exaggerated θ - δ EEG in cats anesthetized with various agents in our previous study (26). As the present study was performed under conditions of ongoing surgery, the degree to which surgical noxious stimulation contributed to the electroencephalographic changes could not be evaluated. However, the fact that the electroencephalographic pattern transformation followed a more or less uniform evolution suggests that, although the surgical stimula-

Figure 4. Induction of δ-wave EEG by surgical noxious stimulation followed by stage 3 spindle-type EEG. When the surgeons pulled the intestine, a δ-wave EEG appeared; it disappeared within 3 min (patient 10).

tion might have exaggerated the electroencephalographic changes by N_2O , it was of secondary significance to the actions proper to N_2O .

Although there are reports of awareness and pain experience during anesthesia (31,32), it is our personal experience that awareness during N_2O anesthesia is not associated with pain perception. The absence of acute tolerance to N_2O analgesia has already been confirmed in rats by this laboratory (33). The possible correlation between awareness and electroencephalographic changes observed in the present study requires further clarification.

In summary, using the electroencephalographic responses to N_2O the present study demonstrated the occurrence of progressive changes in the CNS response to N_2O in humans. The altered CNS responsiveness was maintained for 30 min after withdrawal of N_2O . These findings are consistent with the concept of development of acute tolerance to N_2O in humans.

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Efficacy of High-Frequency Jet Ventilation in Cardiac Tamponade

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GOTO K, GOTO H, BENSON KT, UNRUH GK, ARAKAWA K. Efficacy of high-frequency jet ventilation in cardiac tamponade. Anesth Analg 1990;70:375–81.

To evaluate the effects of high-frequency jet ventilation (HFJV) (f=60, 120 breaths/min) and conventional mechanical ventilation (CMV) (f=10, 20) during equivalent conditions of cardiac tamponade, stroke index (SI), intrapericardial pressure (IPP), airway pressure (P_{aw}), and cardiac pressures were measured in anesthetized, paralyzed, chest-closed dogs with the same levels of Paco₂. Cardiac tamponade was produced by infusing normal saline into the intrapericardial space to increase IPP to either 8 mm Hg (group 1, n=8) or 12 mm Hg (group 2, n=8). Stroke index in group 1 was 7.3 \pm 0.8 during CMV (f=10), 8.1 \pm 0.7 during CMV (f=20), 10.9 \pm 1.4 during HFJV (f=10)

= 60), and 10.7 \pm 1.2 (mL·beat⁻¹·m⁻²) during HFJV (f = 120). Stroke index in group 2 was 4.1 \pm 0.7, 5.1 \pm 0.5, 7.2 \pm 0.5, and 6.7 \pm 0.5 (mL·beat⁻¹·m⁻²), respectively. In both IPP groups, stroke index values during HFJV were significantly higher than during CMV; however, there were no significant differences in mean left and right atrial transmural pressures between HFJV and CMV. Peak IPP, mean P_{aw}, and peak P_{aw} during HFJV were significantly lower than those during CMV. The results indicate that HFJV with lower mean and peak P_{aw}, and with lower mean and peak IPP, can result in higher cardiac output than CMV in cardiac tamponade. Thus, HFJV may be superior to CMV in the clinical management of cardiac tamponade.

Key Words: HEART, TAMPONADE—ventilation. VENTILATION, HIGH-FREQUENCY JET.

Acute cardiac tamponade caused by an accumulation of fluid in the pericardium or in the surrounding mediastinum is one of the life-threatening complications after open-heart surgery. Spontaneous respiration is generally recommended until pericardial drainage is carried out because intrathoracic pressure is lower and venous return may be better than with positive pressure ventilation (1,2). However, cardiac tamponade often occurs while patients still require respiratory support. Positive pressure ventilation can decrease cardiac output further by decreasing venous return to the heart and by impairing ventricular filling (3). In this situation, mechanical ventilation can cause severe hypotension and even cardiac arrest. Therefore, it is important to determine the optimal mode of ventilation in the presence of cardiac tamponade.

High-frequency jet ventilation (HFJV) is associated

with lower peak and mean airway pressures than is conventional mechanical ventilation (CMV) (4–6); therefore, HFJV may be beneficial in patients with cardiac tamponade. However, the effects of HFJV or CMV at rates over 20 breaths/min in the presence of cardiac tamponade have not been investigated. In this study, the effects of CMV on hemodynamics in anesthetized close-chested dogs with normal lungs but with cardiac tamponade were compared with the effects of HFJV.

Methods

The study was approved by the institutional animal investigation committee of the University of Kansas. Sixteen mongrel dogs (17–24 kg) were anesthetized with intravenous pentobarbital sodium (25 mg/kg) and paralyzed with intravenous pancuronium bromide (0.1 mg/kg), followed by tracheal intubation with a 9-mm-ID cuffed endotracheal tube. The cuff was inflated to achieve a gas-tight fit with the lungs then ventilated with 100% oxygen using a positive pressure ventilator (Foregger 705, Puritan-Bennett, Lenexa, Kan.) at a respiratory rate of 10 breaths/min and an inspiratory to expiratory time ratio of 1:2.

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Tidal volume was adjusted to maintain $Paco_2$ at 35–40 torr. Anesthesia was maintained with an intravenous infusion of pentobarbital sodium (2 $mg \cdot kg^{-1} \cdot h^{-1}$), and paralysis with pancuronium bromide (0.05 $mg \cdot kg^{-1} \cdot h^{-1}$) through the experiment. A lactated Ringer's solution was administered at a constant rate of 5 $mL \cdot kg^{-1} \cdot h^{-1}$.

An 18-gauge cannula was inserted into the femoral artery for arterial pressure measurement and sampling for blood-gas analysis. The blood samples were drawn into heparinized syringes and pH, Pao2, and Paco₂ were measured with an automatic blood-gas analyzer (model 175, Corning, Boston, Mass.). Core temperature was maintained at 37°-38°C with a warming blanket throughout the study. A pulmonary artery flow-directed thermodilution catheter, size 7.5F (SP5507HS, Gould Inc., Oxnard, Calif.), was inserted into the external jugular vein, and its tip was positioned in the pulmonary artery. The catheter was used for measurements of pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure (CVP), and cardiac output by the thermodilution method (model 9520 cardiac output computer, Edwards, Irvine, Calif.). Cardiac outputs were measured three times at each steady state, and the mean was calculated. All pressures were measured with Hewlett-Packard 1290A transducers and Hewlett-Packard 8805B pressure amplifiers. The calibrations were performed using a mercury manometer and checked just before each recording. The pressure data and electrocardiogram were recorded with a polygraph system (7758B, Hewlett-Packard, Palo Alto, Calif.). Airway pressure (Paw) was also monitored using a saline-filled polyethylene catheter (1 mm ID), with its tip located 1 cm distal to the end of the endotracheal tube. The catheter and transducer system showed that the natural frequency was 20 Hz and that the damping coefficient was 0.3 using the flush method (7).

A left thoracotomy incision was made in the fifth intercostal space. A 7F fluid-filled open-ended catheter was inserted into the pericardium for measurement of intrapericardial pressure (IPP) and for induction of tamponade. It was positioned on the anterolateral surface of the left ventricle at the midleft ventricular level and stitched to the pericardium with a purse-string suture. Before insertion into the pericardium, the frequency response of this system was tested using the flush method (7) (natural frequency, 14 Hz; damping coefficient, 0.3). Pericardial suction was applied initially to eliminate trapped air. After the insertion of a closed pleural drain (suction, -5 cm H₂O), the chest incision was closed. The animals were divided into two groups.

In group 1 (n = 8), tamponade was induced by infusing 80-130 mL of saline solution (37°C) at a rate of 3.8 mL/min with use of an infusion pump (model 600-900, Harvard Apparatus Co., Millis, Mass.), producing 8 mm Hg of electronically damped IPP. The IPP was measured during a disconnect of the respiratory circuit for a few seconds (resting IPP). After 60 min of tamponade, each animal underwent four alternating randomized trials of CMV and HFJV. Conventional mechanical ventilation was performed using the positive pressure ventilator (model 705, Foregger) at respiratory rates (f) equal to 10 and 20 breaths/min. The tidal volume was adjusted to maintain Paco2 exactly between 35 and 40 torr. Highfrequency jet ventilation was performed using a highfrequency jet ventilator (VS600, IDC, Pittsburgh, Pa.). The jet injector (2 mm ID) was positioned at the oral end of the endotracheal tube with a jet connector (MERA, Tokyo, Japan), and the side port of the connector was connected to the Y-piece of the semiclosed circuit. For HFJV, the respiratory rate was set at 60 and 120 breaths/min, and Paco, was maintained between 35 and 40 torr by altering the driving pres-

In group 2 (n = 8), the resting IPP was set at 12 mm Hg by infusing 120–250 mL of saline solution. All other procedures were the same as those for group 1.

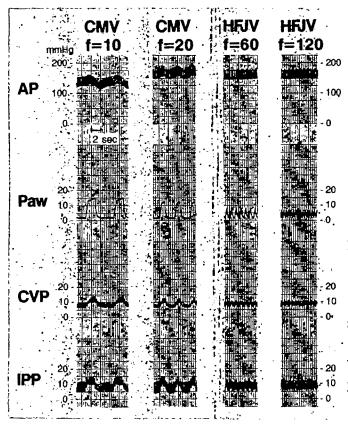
In both groups, the inspiratory to expiratory time ratio was kept constant at 1:2 with both CMV and HFJV. Blood-gas analysis was performed every 15 min and arterial blood pH was maintained at 7.40 \pm 0.05. In group 2, sodium bicarbonate was infused continuously after the induction of tamponade at a rate of 1 mEq·kg⁻¹·h⁻¹. Before changing the ventilatory mode, the resting IPP was checked and readjusted to 8 mm Hg in group 1 and 12 mm Hg in group 2 by infusing a few milliliters of saline into the intrapericardial space if necessary. After maintaining Paco₂ between 35 and 40 torr over 15 min in each ventilatory mode, cardiac output, Paw, electronically damped IPP, and hemodynamic parameters were recorded. Mean pressure values were calculated by integration, and peak IPP values were obtained from the electronically damped IPP.

Body surface area (BSA) in dogs was calculated by the following equation (8):

BSA
$$(m^2) = 0.1 \times W^{0.667}$$
,

where W is the body weight in kilograms. Cardiac index (CI) and stroke index (SI) were calculated as follows:

CI
$$(L \cdot min^{-1} \cdot m^{-2}) = (cardiac \ output)/BSA$$
,
SI $(mL \cdot beat^{-1} \cdot m^{-2}) = CI \times 1000/(heart \ rate)$.



<u>Figure 1</u>. Original recording of arterial pressure, P_{aw} , CVP, and IPP (not electrically damped, actual waves) during CMV and HFJV in group 1. Paper speed is 2.5 mm/s. Note: arterial pressure during CMV decreases at the time P_{aw} and IPP increase.

Data from the four modes of ventilation in groups 1 and 2 were compared using one-way analysis of variance for repeated measurements followed by Scheffé's method (9). Comparisons between data before producing cardiac tamponade and data from each mode of ventilation during cardiac tamponade were made using one-way analysis of variance for repeated measurements followed by Dunnett's test (9). Linear regression analyses were calculated by the method of least squares. Statistical significance was for *P* values < 0.05. All values were reported as mean \pm sem.

Results

Typical original recordings and electronically damped IPP tracings in group 1 are shown in Figures 1 and 2. Hemodynamic changes occurring before and after cardiac tamponade with respect to alternating mode and frequency of ventilation are shown in Table 1 (group 1) and Table 2 (group 2). Calculated mean left and right atrial transmural pressures were defined by mean pulmonary capillary wedge pressure minus mean IPP (L_{tm}) and by mean CVP minus mean IPP

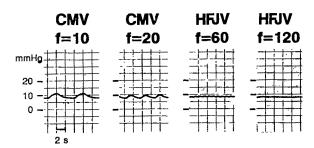


Figure 2. Original recording of electronically damped IPP during CMV and HFJV in group 1. Paper speed is 2.5 mm/s.

(R_{tm}). There were no significant differences in heart rate, Ltm, Rtm, or blood-gas data between CMV and HFJV in both groups. When CMV (f = 10) was compared with CMV (f = 20) in both groups, peak IPP and mean and peak P_{aw} were higher in CMV (f = 10) than in CMV (f = 20), but there was no significant difference in CI. As compared with CMV (f = 10), mean IPP, peak IPP, mean Paw, and peak Paw were lower and CI was significantly higher in HFJV (f = 60) in both groups. Peak IPP, mean Paw, and peak Paw of HFJV (f = 120) were lower and CI was higher than those of CMV (f = 10) in both groups. When CMV (f = 20) was compared with HFJV in both groups, peak IPP, mean P_{aw}, and peak P_{aw} were lower in both HFJV than in CMV (f = 20), but no significant differences were observed in mean IPP between CMV (f = 20) and HFJV (f = 60, 120). In group 1, CI of both HFJV series were higher than those of CMV (f = 20). In group 2, CI of HFJV (f = 60) was higher than that of CMV (f = 20). The only significant difference between HFJV (f = 60) and HFJV (f = 120) was peak P_{aw} in group 1. Figure 3 shows that SI during HFJV (f = 60, 120) was significantly higher than SI during CMV (f = 10, 20).

Discussion

It is generally believed that HFJV can maintain adequate ventilation with a smaller tidal volume and, therefore, mean and peak airway pressures that are lower than in CMV (4–6, 10). In HFJV, increasing the rate can cause an inadvertent end-expiratory pressure (auto-PEEP effect) (11–14). Positive end-expiratory pressure can reduce cardiac output in tamponade (3). Therefore, the ventilatory frequencies of 60 and 120 were used for HFJV in order to minimize the PEEP effect.

The commonly used inspiratory to expiratory time ratio, 1:2, was used with both HFJV and CMV. As inspiratory to expiratory time ratios influence CO_2 elimination, lung volume, and P_{aw} , further studies are needed to address the question of the effect of

Table 1. Hemodynamic Effects of Altering Mode and Frequency of Ventilation in Group 1 (resting IPP = 8 mm Hg)

	Pretamponade	CMV (f = 10)	$ \begin{array}{l} CMV \\ (f = 20) \end{array} $	HFJV (f = 60)	HFJV (f = 120)
Heart rate (beats/min)	177 ± 6	197 ± 3°	208 ± 5^{a}	201 ± 5"	206 ± 3"
Mean AP (mm Hg)	140 ± 5	118 ± 7^{b}	$131 \pm 7^{\circ}$	137 ± 5^d	134 ± 6^d
Mean PAP (mm Hg)	16.2 ± 0.7	16.4 ± 0.4	17.3 ± 0.5	18.1 ± 0.8	17.8 ± 1.0
Mean PCWP (mm Hg)	8.2 ± 0.3	11.1 ± 0.5^{a}	11.2 ± 0.5^{a}	11.0 ± 0.7^a	10.4 ± 0.2^{a}
Mean CVP (mm Hg)	4.1 ± 0.4	8.9 ± 0.1^{a}	8.5 ± 0.2^{a}	$7.7 \pm 0.3^{a_z d_z e}$	$7.9 \pm 0.3^{a,e}$
Mean IPP (mm Hg)	1.9 ± 0.7	9.1 ± 0.2^{a}	8.7 ± 0.2^{a}	$8.2 \pm 0.2^{a,d}$	8.5 ± 0.2^{a}
Peak IPP (mm Hg)	4.1 ± 0.7	11.3 ± 0.5^a	$10.0 \pm 0.2^{a.c}$	$8.5 \pm 0.2^{a,d,f}$	$8.6 \pm 0.2^{a,d,f}$
L _{tm} (mm Hg)	6.3 ± 0.9	2.0 ± 0.5^{a}	2.5 ± 0.5^{a}	2.8 ± 0.7^{a}	1.9 ± 0.3^{a}
R _{tm} (mm Hg)	2.1 ± 0.6	-0.2 ± 0.1^{a}	-0.3 ± 0.3^{b}	-0.5 ± 0.3^{a}	-0.6 ± 0.3^a
Mean Pass (mm Hg)	4.9 ± 0.5	5.1 ± 0.3	4.1 ± 0.3^d	$3.0 \pm 0.3^{a,d,f}$	$2.5 \pm 0.3^{a,d,f}$
Peak P _{aw} (mm Hg)	12.5 ± 1.1	13.5 ± 0.8	$11.0 \pm 0.8^{b,d}$	$7.8 \pm 0.6^{a,d,f}$	$6.4 \pm 0.6^{a,d,f,g}$
CI (L·min ⁻¹ ·m ⁻²)	3.2 ± 0.3	1.4 ± 0.2^{a}	1.7 ± 0.1^a	$2.2 \pm 0.3^{a,d,f}$	$2.2 \pm 0.3^{a,d,f}$
pH	7.40 ± 0.01	7.39 ± 0.01	7.43 ± 0.01	7.42 ± 0.02	7.42 ± 0.01
Paco ₂ (torr)	36 ± 1	36 ± 1	37 ± 1	37 ± 1	37 ± 1
Pao ₂ (torr)	440 ± 38	444 ± 38	428 ± 45	428 ± 46	424 ± 45

AP, arterial pressure; CI, cardiac index; CMV, conventional mechanical ventilation; CVP, central venous pressure; HFJV, high-frequency jet ventilation; IPP, intrapericardial pressure; L_{tm}, left atrial transmural pressure; PAP, pulmonary artery pressure; P_{aw}, airway pressure; PCWP, pulmonary capillary wedge pressure; R_{tm}, right atrial transmural pressure; Values are mean ± SEM.

Table 2. Hemodynamic Effects of Altering Mode and Frequency of Ventilation in Group 2 (resting IPP = 12 mm Hg)

	Pretamponade	CMV (f = 10)	CMV (f = 20)	HFJV (f = 60)	HFJV (f = 120)
Heart rate (beats/min)	189 ± 6	212 ± 7"	216 ± 7^{a}	213 ± 6^{b}	209 ± 8^{a}
Mean AP (mm Hg)	141 ± 4	96 ± 9^{b}	112 ± 10^{a}	$120 \pm 6^{a.c}$	108 ± 7^{6}
Mean PAP (mm Hg)	17.1 ± 0.8	19.3 ± 0.8	19.2 ± 0.7	19.5 ± 0.8	20.0 ± 0.7^a
Mean PCWP (mm Hg)	8.9 ± 0.5	14.4 ± 0.5^{b}	14.3 ± 0.6^{b}	14.4 ± 0.5^{b}	13.7 ± 0.4^b
Mean CVP (mm Hg)	4.6 ± 0.3	12.8 ± 0.3^{b}	12.2 ± 0.2^{b}	$11.7 \pm 0.2^{b.c}$	11.8 ± 0.3^{h}
Mean IPP (mm Hg)	1.7 ± 0.7	13.2 ± 0.2^{b}	12.6 ± 0.1^{b}	$12.0 \pm 0.1^{b,d}$	$12.3 \pm 0.1^{b,d}$
Peak IPP (mm Hg)	4.0 ± 0.8	15.7 ± 0.6^{b}	$13.8 \pm 0.2^{b,d}$	$12.1 \pm 0.1^{b,d,c}$	$12.3 \pm 0.1^{b,d,a}$
L _{sm} (mm Hg)	7.2 ± 0.9	1.2 ± 0.4^{b}	1.7 ± 0.6^{b}	2.4 ± 0.5^{b}	1.5 ± 0.3^{b}
R _{tm} (mm Hg)	2.9 ± 0.6	$-0.4 \pm 0.3^{\prime\prime}$	-0.4 ± 0.2^{b}	-0.3 ± 0.2^{b}	-0.4 ± 0.2^{b}
Mean P _{aw} (mm Hg)	5.1 ± 0.5	5.4 ± 0.4	$4.6 \pm 0.4^{\circ}$	$3.1 \pm 0.3^{b,d,f}$	$3.0 \pm 0.3^{b,d}$
Peak Paw (mm Hg)	12.3 ± 1.1	14.0 ± 1.1	11.1 ± 1.0^d	$7.6 \pm 0.6^{b,d,f}$	$6.5 \pm 0.6^{b,d}$
CI (L·min ⁻¹ ·m ⁻²)	3.1 ± 0.3	0.9 ± 0.2^{b}	1.1 ± 0.1^{b}	$1.5 \pm 0.1^{b.d.e}$	$1.4 \pm 0.1^{b,d}$
pH	7.41 ± 0.01	7.39 ± 0.01	7.43 ± 0.01	7.41 ± 0.01	7.38 ± 0.01
Paco ₂ (torr)	36 ± 1	36 ± 1	36 ± 1	37 ± 1	36 ± 1
Pao ₂ (torr)	471 ± 39	427 ± 38	445 ± 34	462 ± 34	450 ± 39

See footnote to Table 1 for abbreviations

inspiratory to expiratory time ratio in cardiac tampon-

A previous study by Smiseth et al. (15) has shown that a balloon-tipped catheter is more accurate than a fluid-filled open-ended catheter in measuring IPP. This is true only when there is a small amount of fluid in the intrapericardial space (15). We confirmed in a preliminary study that the fluid-filled open-ended catheter reflects the IPP as accurately as a balloontipped catheter when a considerable amount of pericardial fluid (over 50 mL) is present (15). In our studies, it required more than 80 mL of saline to create cardiac tamponade with resting IPP levels of 8 and 12 mm Hg. As pericardial incisions might substantially alter overall cardiac filling behavior, we selected the fluid-filled open-ended catheter so that the incision in the pericardium could be very small.

Intrapericardial pressure may vary depending on the site of the catheter tip in the pericardium. The catheter tip was always placed on the anterolateral surface of the left ventricle at the mid-left ventricular level. Resting IPP, measured during apnea by discon-

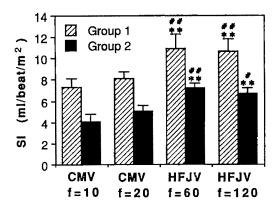
 $[^]a(P<0.01), ^b(P<0.05)$, significantly different from pretamponade $^c(P<0.05), ^d(P<0.01)$, significantly different from CMV (f = 10).

P(P < 0.05), P(P < 0.01), significantly different from CMV (f = 20).

g(P < 0.05), significantly different from HFJV (f = 60).

 $[^]a(P<0.05), ^b(P<0.01)$, significantly different from pretamponade. $^c(P<0.05), ^d(P<0.01)$, significantly different from CMV (f = 10).

 $^{^{}c}(P < 0.05)$, $^{f}(P < 0.01)$, significantly different from CMV (f = 20).

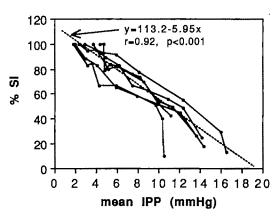


<u>Figure 3</u>. Changes of SI induced by altering mode and frequency of ventilation in cardiac tamponade, groups 1 and 2. **P < 0.01 vs CMV (f = 10) within each group; *P < 0.05, **P < 0.01 vs CMV (f = 20) within each group.

necting the respiratory circuit for a few seconds, was precisely maintained at 8 and 12 mm Hg by checking every 15 min and just before changing ventilatory modes throughout the experiments.

It is generally believed that the major functional disturbance caused by cardiac tamponade is a mechanical restriction of atrial and ventricular filling (16–17). This results in a reduction in stroke volume and cardiac output. In contrast to spontaneous breathing, CMV increases the inspiratory airway pressure and the intrathoracic pressure, which can be transmitted to the intrapericardial space, and accentuates the effects of cardiac tamponade (3,18). Mattila et al. (18) reported that a ventilation frequency of 12 with higher P_{aw} levels produced further decreases in cardiac output and systemic arterial pressure, compared to a ventilation frequency of 20 with lower P_{aw}.

The experimental design in the present study made it possible to compare the hemodynamic effects of HFJV with those of CMV during equivalent conditions of cardiac tamponade of 8 and 12 mm Hg IPP. The results clearly show that the reduction of CI and SI with HFJV was significantly less than with CMV in both groups. Although CMV decreased CI and SI more than HFJV, presumably by decreasing venous return and cardiac filling, there were no significant differences in calculated right and left atrial transmural pressures (Tables 1 and 2). Tyberg et al. (19) reported that IPP was very close to right atrial pressure over a wide range of IPP values. If this were true, the right atrial transmural pressure calculated by CVP minus IPP would be approximately equal to zero; therefore, the right heart preload cannot accurately be estimated by the right transmural pressure calculated as above. This probably explains the difference in CI and SI values between CMV and HFJV despite the same calculated transmural pressure.



<u>Figure 4</u>. The relationships between mean IPP and percentage changes of SI (%SI) during continuous saline infusion into the pericardial space (3.8 mL/min) without changing respiratory rate and tidal volume during producing tamponade (CMV, f = 10).

Fewell et al. (20) reported that the increase of intrapleural pressure caused by hyperinflation of the lung decreased right and left end-diastolic volumes without changing either transmural end-diastolic pressure or cardiac contractility, and concluded that hyperinflation of the lung decreases cardiac output by decreasing preload. Thus, the calculated transmural pressure including our data may not necessarily reflect the actual cardiac preload.

It is generally believed that mean IPP rather than peak IPP affects cardiac function. In our preparatory experiments, we confirmed that SI decreased linearly with increasing mean IPP during positive pressure ventilation (Figure 4). However, mean IPP alone may not be sufficient to explain differences of CI and SI among four modes of ventilation. For instance, there were significant differences between CMV (f = 20) and HFJV (f = 60) in peak IPP and SI, but not in mean IPP (Tables 1 and 2; Figure 3). This suggests that peak IPP, which is reflecting peak P_{aw} , plays an important role in reducing stroke volume. As shown in Figures 1 and 2, the increases in IPP and CVP caused by inspiration were minimal during HFJV. This indicates that the lower peak Paw during HFJV is transmitted less to the intrapericardial space than is the higher peak Paw during CMV, resulting in less adverse impact on cardiac performance. It has been reported that in acute respiratory failure with circulatory shock, mean arterial pressure and cardiac output are higher during HFJV than during CMV despite the fact that the mean P_{aw} and Paco₂ were the same (21). This report may support our finding that peak Paw affects SI more significantly than mean Paw. In addition to mean IPP and peak IPP, it is obvious that the duration of increased IPP within the respiratory cycle is an important factor, one that determines the decrease in SI.

Table 3. Intrapericardial Compression Index of Altering Mode and Frequency of Ventilation in Cardiac Tamponade

	Pretamponade	CMV (f = 10)	CMV (f = 20)	HFJV (f = 60)	HFJV (f = 120)
Group 1 Group 2	11.4 ± 3.3 8.1 ± 3.3	102.9 ± 6.6^{a} 143.4 ± 7.8^{a}	87.6 ± 3.9^a 120.6 ± 3.0^a	$69.9 \pm 3.0^{a,b,c}$ $99.6 \pm 2.1^{a,b,c}$	$73.5 \pm 2.7^{a,b,c}$ $104.7 \pm 2.7^{a,b}$

CMV, conventional mechanical ventilation; HFJV, high-frequency jet ventilation; ICI, intrapericardial compression index; IPP, intrapericardial pressure.

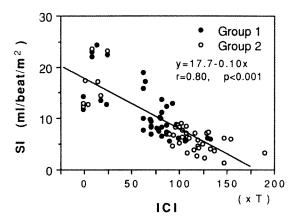


Figure 5. The negative correlation between SI and ICI (intrapericardial compression index). See details in text.

Therefore, the mechanism of reduction of SI by mechanical ventilation during cardiac tamponade includes three factors: (a) mean IPP; (b) peak IPP; and (c) the time factor (T) of the effective compression during the respiratory cycle. We are introducing a new index (intrapericardial compression index, ICI) defined by the following equation:

$$ICI = (mean IPP) \times (peak IPP) \times T.$$

In Table 3, the differences in ICI between four modes of ventilation were closely in agreement with those of CI and SI. Figure 5 shows a significant negative correlation between SI and ICI. This result indicates that peak IPP is as important a factor in limiting the stroke volume as mean IPP during mechanical ventilation. As mean IPP and peak IPP are reflecting mean Paw and peak Paw, HFJV with lower mean and peak P_{aw} can result in higher cardiac output than CMV in tamponade.

Our study indicates not only that HFJV may be superior to CMV in cases of cardiac tamponade when assisted or controlled ventilation is required, but also that smaller tidal volumes and higher respiratory rates should be chosen, even with conventional ventilation, in order to minimize the risk of cardiogenic shock.

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ICI = mean IPP \times peak IPP \times time factor (T). Values are mean \pm sem.

 $[^]a(P < 0.01)$, significantly different from pretamponade within each group. $^b(P < 0.01)$, significantly different from CMV (f = 10) within each group. $^c(P < 0.05)$, significantly different from CMV (f = 20) within each group.

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Cardiovascular and Neuromuscular Effects of Three Steroidal Neuromuscular Blocking Drugs in Dogs (ORG 9616, ORG 9426, ORG 9991)

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CASON B, BAKER DG, HICKEY RF, MILLER RD, AGOSTON S. Cardiovascular and neuromuscular effects of three steroidal neuromuscular blocking drugs in dogs (ORG 9616, ORG 9426, ORG 9991). Anesth Analg 1990;70:382–8.

Developmental research has been directed toward creating nondepolarizing muscle relaxants with an onset time and duration of actions shorter than that of vecuronium or atracurium. We determined the cardiovascular and neuromuscular effects of three new and promising nondepolarizing muscle relaxants in six dogs anesthetized with halothane. Each dog was anesthetized four times (each time separated from the others by at least 1 wk); one muscle relaxant was studied each time. Three doses (one, three, and five times the ED₉₀) were given as intravenous bolus injections. ORG 9616 and ORG 9991 had shorter durations of action than ORG 9426. The duration of action of the doses that were five times the ED₉₀ was 18 ± 5.88 and 15.8 ± 4.41 min (mean \pm SD) with ORG 9616 and ORG 9991,

respectively, as compared with 39.7 ± 17.15 min with ORG 9426 (P < 0.05). ORG 9426 was virtually free of cardiovascular effects. The ED90 doses of ORG 9616 and ORG 9991 did not cause cardiovascular effects; the doses of three and five times the ED90 caused small decreases in mean arterial blood pressure and increases in heart rate. Mean arterial blood pressure decreased from 99 ± 10.2 to 88 ± 13.1 mm Hg and from 98 ± 11.7 to 77 ± 8.1 mm Hg with five times the ED_{90} dose of ORG 9616 and ORG 9991, respectively. The authors conclude that ORG 9426 has a duration of neuromuscular blockade that is probably similar to vecuronium, and one that is free of cardiovascular effects. ORG 9616 and ORG 9991 have shorter durations of action, but cause decreases in arterial blood pressure and increases in heart rate with larger doses. The extent to which these cardiovascular changes may occur in humans will determine the ultimate clinical efficacy of these drugs.

Key Words: NEUROMUSCULAR RELAXANTS—ORG 9426, ORG 9616, ORG 9991.

A valuable nondepolarizing neuromuscular blocking drug would have a more rapid onset time (i.e., time from administration of the drug until its peak effect) and a shorter duration of action than the currently available drugs vecuronium and atracurium. Furthermore, such a drug would have minimal cardiovascular effects when given in doses providing adequate, rapid paralysis for endotracheal intubation. Recently, efforts to develop neuromuscular blocking drugs with these characteristics have produced three possibili-

ties: ORG 9616, ORG 9426, and ORG 9991, all of which are steroidal blockers (Figure 1). In fact, ORG 9426 and ORG 9616 are currently undergoing clinical trials. To determine the cardiovascular effects of these three new drugs, we made serial measurements of hemodynamics in anesthetized dogs. Although the primary goal of the study was to determine the cardiovascular effects of these drugs, we also monitored their neuromuscular effects.

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Methods

Experimental Preparation

These studies were approved by our Committee on Animal Research. Dogs (19–32 kg) were anesthetized initially by injection of thiopental (20 mg/kg intravenously). The trachea was then intubated, and anesthesia was maintained with 1%–3% halothane in

NAME	R ₁	R ₂	STRUCTURE
Org 9616	Acetyi	Butyryl	OR ₂ OR ₂ R ₁ O Br
Org 9426	н	Acetyl	OR ₂ II Br
Org 9991	Ac ety i	Butyryl	OR ₂ OR ₂ Br

oxygen. The lungs were ventilated mechanically using a constant volume ventilator (Ohio Medical) set at a rate of 8–10 breaths/min and a tidal volume of 15 mL/kg. End-tidal halothane and carbon dioxide concentrations were measured by infrared gas analyzers (Puritan-Bennet), and end-tidal carbon dioxide was maintained at 30–33 mm Hg, a level that abolished all spontaneous respiratory movements.

Under sterile conditions, an 18-gauge Teflon catheter was inserted percutaneously into the left femoral artery for measurement of arterial blood pressure. A triple-lumen pulmonary artery flotation catheter (American Edwards) was inserted percutaneously through the right external jugular vein and was passed into the pulmonary artery to be used for measurements of central venous, pulmonary arterial and pulmonary wedge pressures, as well as for measurements of cardiac output (thermodilution method) and of core body temperature.

To measure muscle twitch tension in the ankle extensor muscles, the dog was secured in the supine position, and the right leg was immobilized from hip to ankle. Using an elastic bandage, the right thigh was tightly wrapped to a well-padded, fixed vertical pole (perpendicular to the long axis of the dog, at hip level). From knee to ankle, the leg was immobilized by wrapping to a fixed horizontal pole (perpendicular

Figure 1. Formulas of ORG 9616, ORG 9426, and ORG 9991.

to the thigh). The tip of the paw was then attached to a force-displacement transducer (Grass Instruments), using a loop of wire that encircled the paw at the level of metatarsal heads. Finally, stimulating needle electrodes were inserted percutaneously so that their exposed tips lay near the sciatic nerve. The sciatic nerve was stimulated at a frequency of 0.3 Hz by a Grass S44 stimulator; the stimulating pulses had a magnitude of 20–30 V (i.e., supramaximal) and a duration of 0.1 ms.

After all measurement devices were secured, the end-tidal halothane concentration was decreased and was held constant thereafter at 1%–1.2%. Before each study commenced, a recovery period of 30–45 min was allowed during which the animal was not stimulated. Body temperature was monitored and maintained throughout the study by adjusting an overhead heating lamp.

Femoral artery, pulmonary artery, pulmonary wedge, and central venous pressures were measured by Statham P23Gb strain gauges. Twitch tension of the tibialis anterior muscle was measured by a Grass force-displacement transducer. Airway carbon dioxide concentration was continuously measured by a Puritan Bennet infrared carbon dioxide monitor. Car-

diac output was measured in triplicate by the thermodilution method using an Edwards 9250 cardiac output computer. Systemic vascular resistance (SVR) was calculated as

$$SVR = \left(\frac{MAP - CVP}{CO}\right) \times 80,$$

where CVP is the central venous pressure, MAP is the mean arterial pressure, and CO is the cardiac output. Heart rate was measured by a Grass tachograph. All measured variables were recorded on a Grass model 7 Polygraph.

Protocol

On separate occasions, the ED_{90} (dose of neuromuscular blocking drug that causes a 90% decrease in twitch tension) was determined by establishing doseresponse curves. Then three different intravenous doses of each muscle relaxant (one, three, and five times the ED_{90}) were tested in each of six dogs. The ED_{90} doses of ORG 9426, ORG 9616, and ORG 9991 were 0.18, 0.22, and 0.26 mg/kg, respectively. Only one drug (three doses) was studied per day, so each dog was studied on three separate days. Additionally, the hemodynamic effects of the drug's solvent were determined in additional studies on five of these dogs.

Solutions of neuromuscular blocking drugs were prepared by mixing the drugs with the solvent supplied to us by Organon, Inc., to make a 10-mg/mL solution. The test solution was injected into the right atrium through a lumen of the pulmonary artery catheter in 2–3 s and was washed in with 1–2 mL of 0.9% NaCl solution. Control injections were made by injecting the equivalent volume of solvent. The latency of the response was measured from the beginning of the injection.

Immediately before and at intervals after injection, arterial blood pressure, heart rate, pulmonary artery pressure, pulmonary artery wedge pressure, central venous pressure, and stimulus-evoked twitch were recorded. In any particular study, the order of the three injections was randomized; the second and third injections were made only after the stimulus-evoked response returned to control levels. If twitch tension did not return at the end of the 30-min recording period, which happened in the case of higher doses of ORG 9426, longer periods were allowed before the next dose was injected. At the end of a particular study, all catheters, the tracheal cannula, and stimulating electrodes were removed, halothane was discontinued, and the dog was al-

Table 1. Neuromuscular Effects of ORG 9426, ORG 9616, and ORG 9991 (mean \pm sp)

	`	<u></u> '	
	$1 \times ED_{90}$	$3 \times ED_{90}$	$5 \times ED_{90}$
ORG 9426			
Onset	1.1 ± 0.49	0.8 ± 0.49	0.5 ± 6.24^{b}
Duration	$13.7 \pm 7.35^{\circ}$	$31.5 \pm 15.90^{a,b}$	$39.7 \pm 17.15^{a,b}$
Recovery	9.7 ± 1.96	9.8 ± 3.92	11.2 ± 4.65
ORG 9616			
Onset	1.7 ± 0.73	1.0 ± 0.73	0.9 ± 0.73
Duration	5.9 ± 2.94	10.7 ± 3.43^{b}	18.0 ± 5.88^{b}
Recovery	4.3 ± 2.63	6.0 ± 1.96	6.3 ± 2.69
ORG 9991			
Onset	1.3 ± 0.49	1.0 ± 0.49	0.8 ± 0.73
Duration	7.1 ± 1.71	11.5 ± 2.69^b	15.8 ± 4.41^{b}
Recovery	2.7 ± 0.49	4.5 ± 0.73^{b}	7.2 ± 3.43^{b}

 $\rm ED_{90}$, dose required to depress twitch tension by 90%; onset, time (min) to maximum response; duration, time (min) to 20% recovery; recovery, time (min) from 25% to 75% recovery.

"Significant difference (P < 0.05) from same dose of ORG 9616 or ORG 9991.

^bSignificant difference (P < 0.05) from $1 \times ED_{90}$.

lowed to awaken. Another experiment was begun only after full recovery (1–3 wk later).

Analysis of Data

All pressures, heart rate, cardiac output, systemic vascular resistance, and stroke volume were measured at end-expiration, immediately before and at intervals (2, 5, 10, 15, 20, 25, and 30 min) after injection of the neuromuscular blocker solution of solvent. Values were expressed either in appropriate units (i.e., mm Hg) or as a percent of control. Hemodynamic data were analyzed using analysis of variance with repeated measures. For comparison of neuromuscular effects between drugs, a one-way analysis of variance was performed. When multiple comparisons were indicated by analysis of variance results, the Scheffé S-test was used. All data were reported as mean \pm one standard deviation.

Results

Both ORG 9616 and ORG 9991 had shorter durations of action when compared with ORG 9426 (P < 0.05) (Table 1). Recovery times (time from 25% to 75% recovery of twitch tension) were not different among the three neuromuscular blockers. Durations of action were directly related to the dose of neuromuscular blocking drug given.

There were no significant cardiovascular changes with the solvent (Table 2) or the ED_{90} blocking doses

<u>Table 2</u>. Cardiovascular Effects of the Solvent (mean \pm sp) (n = 6)

Min	HR	MAP	PAP	PAWP	CVP	CO	SVR
0	101 ± 8.7	100 ± 12.8	19 ± 2.5	13 ± 0.8	4 ± 2.1	3.3 ± 0.55	2463 ± 685.9
2	99 ± 8.5	100 ± 12.7	19 ± 3.7	13 ± 1.1	4 ± 1.8	3.4 ± 0.44	2369 ± 730.1
5	100 ± 7.5	100 ± 12.7	19 ± 2.5	13 ± 1.3	4 ± 1.9	3.4 ± 0.57	2300 ± 608.5
10	100 ± 6.9	100 ± 12.7	19 ± 2.6	13 ± 1.3	4 ± 1.9	3.6 ± 0.53	2246 ± 531.4
15	100 ± 6.7	100 ± 11.4	19 ± 2.6	13 ± 1.3	4 ± 1.9	3.6 ± 0.61	2274 ± 565.4
20	100 ± 6.7	100 ± 10.6	19 ± 1.8	13 ± 1.6	4 ± 2.1	3.5 ± 0.53	2284 ± 529.4
25	100 ± 7.3	100 ± 9.4	19 ± 1.8	13 ± 1.6	5 ± 2.1	3.5 ± 0.72	2277 ± 590.8
30	100 ± 6.9	99 ± 10.2	20 ± 1.9	13 ± 1.6	4 ± 2.1	3.6 ± 0.65	2224 ± 471.9

CO, cardiac output (L/min); CVP, central venous pressure (mm Hg); HR, heart rate (beats/min); MAP, mean arterial blood pressure (mm Hg); Min, minutes after injection of the solvent; PAP, pulmonary artery pressure (mm Hg); PAWP, pulmonary artery wedge pressure (mm Hg); and SVR, systemic vascular resistance (dynes-s-cm⁻⁵).

<u>Table 3</u>. Cardiovascular Effects of Three Doses of ORG 9426 (mean \pm sp)

Min	HR	MAP	PAP	PAWP	CVP	CO	SVR
			1	× ED ₉₀			
0	109 ± 10.1	90 ± 11.7	11 ± 3.1	4 ± 1.5	4 ± 1.0	3.5 ± 1.24	2151 ± 687.6
2	111 ± 7.9	91 ± 10.9	12 ± 4.0	10 ± 1.6	4 ± 0.8	3.7 ± 1.48	2092 ± 691.7
5	112 ± 6.4	91 ± 10.9	12 ± 3.8	10 ± 1.5	4 ± 0.8	3.9 ± 1.56	2026 ± 715.1
10	111 ± 5.6	90 ± 10.6	12 ± 3.9	10 ± 1.6	4 ± 0.7	3.9 ± 1.60	1992 ± 706.6
15	114 ± 6.5	89 ± 10.4	13 ± 3.1	10 ± 1.2	5 ± 0.8	4.0 ± 1.81	1974 ± 831.2
20	115 ± 7.1	88 ± 9.3	12 ± 3.4	11 ± 1.4	5 ± 0.8	4.1 ± 1.92	1908 ± 803.3
25	116 ± 8.9	88 ± 9.2	12 ± 3.4	10 ± 1.2	5 ± 0.8	4.2 ± 2.21	1879 ± 795.2
30	117 ± 8.6	88 ± 9.3	13 ± 3.4	11 ± 1.1	5 ± 0.8	4.1 ± 1.99	1872 ± 666.2
			3	× ED ₉₀			
0	109 ± 11.4	89 ± 12.0	12 ± 3.2	10 ± 1.1	4 ± 0.7	3.5 ± 1.12	2020 ± 554.6
2	113 ± 13.0	92 ± 10.1	12 ± 3.3	10 ± 1.1	4 ± 0.7	3.6 ± 1.01	2069 ± 430.6
5	114 ± 12.7	90 ± 10.8	12 ± 3.0	10 ± 1.4	4 ± 0.7	3.7 ± 1.17	1993 ± 505.0
10	114 ± 12.2	90 ± 10.6	12 ± 2.7	10 ± 1.0	5 ± 1.0	3.8 ± 1.35	1971 ± 568.1
15	112 ± 10.5	89 ± 10.7	12 ± 3.0	10 ± 1.2	5 ± 0.8	3.8 ± 1.27	1956 ± 554.5
20	112 ± 9.9	89 ± 9.7	12 ± 3.1	10 ± 1.2	5 ± 0.6	3.8 ± 1.42	1954 ± 608.6
25	112 ± 9.8	88 ± 9.8	12 ± 3.3	10 ± 1.2	5 ± 0.7	3.8 ± 1.27	1916 ± 575.6
30	112 ± 9.0	89 ± 8.9	13 ± 3.4	11 ± 1.5	5 ± 0.8	3.9 ± 1.37	1883 ± 592.3
			5	× ED ₉₀			
0	109 ± 8.5	92 ± 7.6	13 ± 3.4	11 ± 1.5	5 ± 0.8	3.8 ± 2.1	2179 ± 777.2
2	112 ± 5.7	93 ± 11.9	13 ± 3.3	11 ± 1.8	5 ± 0.8	3.6 ± 1.32	2160 ± 627.7
5	113 ± 7.0	92 ± 13.6	13 ± 3.4	11 ± 1.7	5 ± 0.8	3.6 ± 1.23	2088 ± 586.7
10	115 ± 8.2	91 ± 12.6	13 ± 3.5	11 ± 1.0	5 ± 1.0	3.8 ± 1.47	2038 ± 666.8
15	120 ± 13.1	91 ± 12.6	13 ± 3.4	11 ± 1.2	5 ± 1.2	4.0 ± 1.71	1992 ± 673.5
20	123 ± 18.7°	90 ± 9.9	13 ± 3.4	11 ± 1.3	5 ± 1.1	4.4 ± 2.15	1843 ± 680.0
25	$123 \pm 18.2^{\circ}$	90 ± 9.6	13 ± 3.0	11 ± 1.3	5 ± 0.9	4.4 ± 2.17	1843 ± 693.3
30	122 ± 14.4^a	91 ± 13.1	13 ± 3.0	11 ± 1.1	6 ± 1.0	4.4 ± 2.09	1799 ± 666.8

CVP, central venous pressure (mm Hg); CO, cardiac output (L/min); ED_{90} , dose required to depress twitch tension by 90%; HR, heart rate; MAP, mean arterial blood pressure (mm Hg); Min, minutes after injection of the solvent; PAP, pulmonary artery pressure (mm Hg); PAWP, pulmonary artery wedge pressure (mm Hg); and SVR, systemic vascular resistance (dynes-s-cm⁻⁵).

*P < 0.05 as compared with time 0.

of any of three neuromuscular blockers (Tables 3–5). With ORG 9426 there were no changes with the dose that was three times the ED₉₀. However, with the dose that was five times the ED₉₀, mean heart rate increased slightly, between 15 and 30 min after administration of the drug (Table 3). In contrast, ORG 9616 produced significant cardiovascular changes. With the dose that was three times the ED₉₀, mean arterial blood pressure and systemic vascular resistance decreased 2 and 5 min after drug administration

(P < 0.05) (Table 4). With the largest dose (5 × ED₉₀), mean arterial blood pressure and systemic vascular resistance decreased starting 2 min after drug administration. Cardiac output increased at 5 min and mean arterial pressure decreased at 2 min after drug administration (P < 0.05) (Table 4).

ORG 9991 caused similar cardiovascular changes as ORG 9616 but to a greater degree. With the intermediate dose (3 \times ED₉₀), mean arterial blood pressure and systemic vascular resistance decreased 2

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Table 4. Cardiovascular Effects of Three Doses of ORG 9616 (mean ± sp)

Min	HR	MAP	PAP	PAWP	CVP	CO	SVR
				× ED ₉₀			
0	110 ± 7.6	94 ± 7.5	12 ± 3.5	12 ± 3.5	6 ± 2.0	3.7 ± 1.59	2450 ± 1535.0
2	111 ± 7.9	93 ± 5.9	11 ± 3.8	11 ± 3.8	6 ± 2.0	4.0 ± 1.70	2350 ± 1856.4
5	109 ± 8.3	94 ± 4.6	12 ± 3.9	12 ± 3.9	6 ± 2.0	3.9 ± 1.73	2270 ± 1583.2
10	110 ± 8.2	95 ± 3.9	12 ± 3.5	12 ± 3.5	6 ± 1.8	3.9 ± 1.55	2227 ± 1399.2
15	110 ± 8.2	92 ± 7.5	12 ± 3.4	12 ± 3.4	6 ± 1.9	4.0 ± 1.71	2200 ± 1258.2
20	109 ± 8.6	98 ± 6.8	13 ± 3.3	13 ± 3.3	6 ± 2.2	3.8 ± 1.55	2292 ± 1278.0
25	110 ± 8.7	96 ± 8.1	13 ± 3.3	13 ± 3.3	7 ± 2.3	3.8 ± 1.57	2309 ± 1206.5
30	110 ± 8.2	96 ± 8.6	12 ± 4.0	12 ± 4.0	7 ± 2.3	3.8 ± 1.49	2224 ± 1115.9
			3	$3 \times ED_{90}$			
0	111 ± 9.6	102 ± 8.1	12 ± 4.2	12 ± 4.1	6 ± 2.8	3.5 ± 1.21	2421 ± 1018.9
2	111 ± 6.9	$96 \pm 9.4^{\circ}$	12 ± 4.2	12 ± 4.2	5 ± 2.4	3.8 ± 1.28	$1997 \pm 782.9^{\circ}$
5	115 ± 7.4	94 ± 11.9^{a}	11 ± 3.7	11 ± 3.7	5 ± 2.0	4.2 ± 1.49	$1917 \pm 843.9^{\circ}$
10	114 ± 9.1	98 ± 10.2	11 ± 3.7	11 ± 3.7	5 ± 1.9	4.1 ± 1.60	2029 ± 756.1
15	113 ± 9.9	104 ± 9.7	12 ± 4.1	12 ± 4.1	6 ± 2.0	4.0 ± 1.50	2121 ± 706.4
20	114 ± 8.0	98 ± 9.1	11 ± 3.8	11 ± 3.8	6 ± 2.4	3.9 ± 1.52	2107 ± 634.9
25	113 ± 7.6	99 ± 9.1	11 ± 3.7	12 ± 3.7	6 ± 2.1	4.1 ± 1.44	2011 ± 620.6
30	113 ± 7.3	97 ± 9.7	12 ± 3.5	12 ± 3.5	6 ± 2.1	3.9 ± 1.24	2038 ± 624.3
			5	× ED ₉₀			
0	110 ± 11.3	99 ± 10.2	19 ± 3.4	11 ± 3.4	6 ± 2.0	3.8 ± 1.42	2285 ± 879.7
2 5	110 ± 12.2	91 ± 12.9^{a}	19 ± 3.2	11 ± 3.2	6 ± 2.0	4.2 ± 1.27	1726 ± 567.8^{a}
5	116 ± 4.3	88 ± 13.1^{a}	20 ± 3.2	12 ± 3.2	6 ± 2.0	4.8 ± 1.48^{a}	1441 ± 505.2^a
10	$119 \pm 4.1''$	95 ± 14.1^{a}	20 ± 3.0	12 ± 3.0	6 ± 2.1	4.9 ± 1.61^a	1643 ± 487.3^{a}
15	120 ± 0.4^{a}	95 ± 12.3	20 ± 3.1	12 ± 3.1	6 ± 2.1	$4.7 \pm 1.43^{\circ}$	1606 ± 432.2^{a}
20	118 ± 1.9^{a}	96 ± 12.8	20 ± 3.7	12 ± 3.7	6 ± 1.9	4.7 ± 1.32^{a}	$1643 \pm 411.0^{\circ}$
25	116 ± 5.1^{a}	94 ± 10.5	20 ± 3.8	12 ± 3.8	6 ± 1.9	4.6 ± 1.36^{a}	1676 ± 468.9^{a}
30	$113 \pm 9.0^{\circ}$	94 ± 10.2	20 ± 3.7	12 ± 3.7	6 ± 1.9	4.4 ± 1.17^a	$1757 \pm 401.3^{\circ}$

CO, cardiac output (L/min); CVP, central venous pressure (mm Hg); ED_{90} , dose required to depress twitch tension by 90%; HR, heart rate; MAP, mean arterial blood pressure (mm Hg); Min, minutes after injection of the solvent; PAP, pulmonary artery pressure (mm Hg); PAWP, pulmonary artery wedge pressure (mm Hg); and SVR, systemic vascular resistance (dynes-s-cm⁻⁵).

"P < 0.05 as compared with time 0.

min after drug administration (Table 5). With the largest dose (5 \times ED₉₀), mean arterial blood pressure and systemic vascular resistance decreased while heart rate increased (Table 5).

To determine the influence of control heart rate (i.e., predrug heart rate), the maximum change in heart rate was correlated with control heart rate with the doses that were three and five times the ED₉₀ with ORG 9991 and ORG 9616. There was a weak but significant correlation between control heart rate and absolute heart rate change (r = 0.485, P < 0.05) (Figure 2).

Discussion

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Our studies show that ORG 9616 and ORG 9991 have a shorter duration of neuromuscular blocking action than that of ORG 9426. All three drugs have been shown in several animal species to have a more rapid onset time than that of vecuronium (Booij LHDJ, Crul JF, Agoston S. Cardiovascular and neuromuscular blocking effects of two new nondepolarizing muscle

relaxants in anesthetized beagle dogs and two species of monkeys. Organon confidential files) (1,2). ORG 9426 has a pharmacokinetic profile and duration of neuromuscular blockade similar to that of vecuronium (2–4), with most of ORG 9426 being sequestered in the liver or eliminated into the bile in an unchanged (i.e., no metabolism) form. In contrast, ORG 9616 is extensively metabolized and excreted into the bile, but about 40% of its clearance is due to a metabolic or elimination pathway yet to be determined (4). Perhaps this unidentified pathway accounts for the rapid clearance of ORG 9616 from plasma and its subsequent short duration of action. Pharmacokinetic studies with ORG 9991 are currently being undertaken.

Our study was designed in a manner similar to that of Booij et al. (3) in that equipotent doses of neuromuscular blocking drugs were studied and each dog served as its own control—i.e., each dog received the solvent alone and all three doses of each neuromuscular blocking drug. Large doses were studied (three and five times the ED₉₀) to ensure that any subtle cardiovascular change would likely be identi-

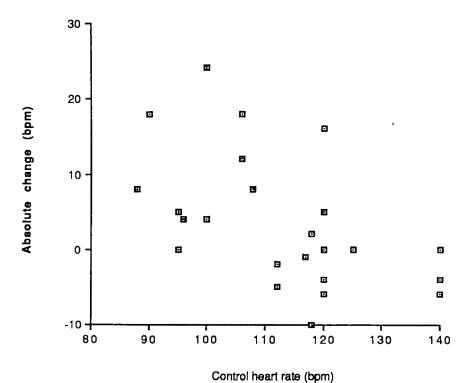
Table 5. Cardiovascular Effects of Three Doses of ORG 9991 (mean \pm sp)

Min	HR	MAP	PAP	PAWP	CVP	CO	SVR
				× ED ₉₀			
0	114 ± 19.1	98 ± 22.5	18 ± 2.1	11 ± 1.8	5 ± 1.8	3.5 ± 1.13	2204 ± 499.3
2	115 ± 19.3	93 ± 19.4	18 ± 1.5	11 ± 1.8	5 ± 1.6	3.7 ± 1.23	1989 ± 389.9
5	116 ± 19.1	94 ± 18.6	18 ± 1.7	11 ± 1.9	5 ± 1.6	3.7 ± 1.17	1976 ± 396.4
10	116 ± 20.1	95 ± 17.9	18 ± 1.9	11 ± 2.0	5 ± 1.6	3.8 ± 1.08	1972 ± 376.1
15	117 ± 18.8	95 ± 18.0	18 ± 2.0	11 ± 2.0	5 ± 1.6	3.7 ± 1.11	1998 ± 286.7
20	118 ± 19.2	95 ± 17.2	18 ± 2.0	12 ± 2.9	5 ± 1.4	3.9 ± 1.06	1885 ± 296.5
25	117 ± 18.4	95 ± 17.6	18 ± 1.7	11 ± 2.1	5 ± 1.6	4.0 ± 1.17	1889 ± 314.1
30	117 ± 18.4	95 ± 16.8	18 ± 1.6	11 ± 1.9	5 ± 1.6	4.0 ± 1.21	1890 ± 389.8
			3	$3 \times ED_{90}$			
0	118 ± 20.3	97 ± 14.1	18 ± 1.7	11 ± 2.2	5 ± 2.7	3.9 ± 1.42	2073 ± 706.8
	118 ± 19.7	83 ± 9.3"	17 ± 0.8	9 ± 1.7	4 ± 2.7	4.3 ± 1.70	$1585 \pm 586.4^{\circ}$
2 5	118 ± 19.7	87 ± 13.7*	17 ± 0.8	10 ± 1.0	5 ± 2.6	4.2 ± 1.50	1717 ± 627.7
10	118 ± 18.7	90 ± 15.0	17 ± 1.0	10 ± 1.2	5 ± 2.2	4.3 ± 1.61	1779 ± 496.6
15	118 ± 19.3	92 ± 14.5	18 ± 1.4	11 ± 1.8	5 ± 2.2	4.2 ± 1.49	1773 ± 541.7
20	120 ± 19.6	92 ± 14.5	18 ± 1.4	11 ± 1.6	5 ± 2.0	4.3 ± 1.53	1731 ± 478.6
25	120 ± 20.6	92 ± 14.5	18 ± 1.8	11 ± 1.5	5 ± 2.2	4.6 ± 1.67	1649 ± 419.3
30	120 ± 20.4	92 ± 14.5	18 ± 1.9	11 ± 1.3	5 ± 2.2	4.5 ± 1.69	1700 ± 457.7
			ŗ	$5 \times ED_{90}$			
0	113 ± 18.6	98 ± 11.7	17 ± 2.0	11 ± 2.1	4 ± 1.9	3.9 ± 1.62	2376 ± 1517.8
2	115 ± 16.2	$77 \pm 8.1^{\circ}$	16 ± 1.3	11 ± 2.4	4 ± 1.8	4.1 ± 1.49	$1687 \pm 965.2^{\circ}$
2 5 ·	$117 \pm 18.4^{\circ}$	79 ± 9.7*	16 ± 1.4	11 ± 2.2	4 ± 1.9	4.0 ± 1.54	1778 ± 1038.44
10	$117 \pm 18.9^{\circ}$	$88 \pm 10.3^{\circ}$	17 ± 0.9	11 ± 2.7	4 ± 2.0	4.0 ± 1.41	$1910 \pm 827.3^{\circ}$
15	117 ± 20.7°	91 ± 11.6	18 ± 1.4	12 ± 4.1	5 ± 2.2	4.0 ± 1.34	1916 ± 739.0°
20	$117 \pm 20.3^{\circ}$	92 ± 12.0	18 ± 1.5	12 ± 4.2	5 ± 2.0	4.0 ± 1.30	$1937 \pm 701.9^{\circ}$
25	118 ± 20.2^{a}	92 ± 12.7	18 ± 1.2	12 ± 3.8	5 ± 2.0	4.2 ± 1.51	$1881 \pm 744.8^{\circ}$
30	$118 \pm 20.6^{\circ}$	92 ± 12.7	18 ± 1.4	12 ± 4.1	5 ± 2.3	4.2 ± 1.54	1887 ± 678.8^{a}

CO, cardiac output (L/min); CVP, central venous pressure (mm Hg); $\rm ED_{90}$, dose required to depress twitch tension by 90%; HR, heart rate; MAP, mean arterial blood pressure (mm Hg); Min, minutes after injection of the solvent; PAP, pulmonary artery pressure (mm Hg); PAWP, pulmonary artery wedge pressure (mm Hg); and SVR, systemic vascular resistance (dynes-s-cm⁻⁵).

*P < 0.05 as compared with time 0.

Figure 2. Correlation between resting heart rate and maximum change in heart rate with three and five times the ED_{90} doses of ORG 9616 and ORG 9991.



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fied. Lastly, the experimental conditions were monitored and carefully controlled, for example, through anesthetic concentration.

ORG 9426 has minimal cardiovascular effects, if any, which, with its pharmacokinetic profile, makes it similar to vecuronium (2,3). In fact, Muir et al. (2) found that the ratio between ganglion and neuromuscular blocking activity was 20. In contrast, ORG 9616 and ORG 9991 produce cardiovascular changes in a dose-dependent manner so that with the largest doses (5 \times ED₉₀), heart rate and cardiac output increased, whereas arterial blood pressure and systemic vascular resistance decreased. Muir et al. (1) found that ORG 9616, in a dose three times the ED₉₀ blocking dose, did not alter arterial blood pressure in the cat and produced a decrease in blood pressure in the pig. Our larger dose (5 \times ED₉₀) obviously would be more likely to cause cardiovascular changes. Our results are compatible with a systemic vasodilatory effect that could be accounted for by several mechanisms, including histamine release or ganglionic blockade. Although our descriptive study only allows speculation regarding the mechanism of these cardiovascular changes, the changes are small; they appear to be comparable to what Booij et al. (3) found with metocurine using experimental conditions similar to ours. However, basic research with these neuromuscular blocking drugs indicates that histamine release and/or ganglionic blockade are unlikely to explain these cardiovascular changes, whereas ORG 9616 is a potent blocker of recepto- and voltage-operated calcium channels in vascular smooth muscle (Marshall

RJ. Organon confidential files. Quoted with permission of RJ Marshall.).

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In summary, we found that ORG 9426 has little or no cardiovascular effects and a duration of neuromuscular blockade probably similar to that of vecuronium. In contrast, ORG 9616 and ORG 9991 have durations of neuromuscular blockade that are markedly shorter than that of ORG 9426 and thus probably that of vecuronium as well. However, large doses (3 and 5 \times ED $_{90}$) of ORG 9616 and ORG 9991 do cause small decreases in arterial blood pressure and increases in heart rate. The extent to which these cardiovascular changes manifest themselves in humans will determine the ultimate clinical efficacy of these short acting neuromuscular blocking drugs.

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Incidence and Prediction of Postdural Puncture Headache A Prospective Study of 1021 Spinal Anesthesias

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LYBECKER H, MØLLER JT, MAY O, NIELSEN HK. Incidence and prediction of postdural puncture headache: a prospective study of 1021 spinal anesthesias. Anesth Analg 1990;70:389–94.

The incidence of postdural puncture headache (PDPH) was investigated prospectively in 873 consecutive patients undergoing a total of 1021 spinal anesthesias, and its association to age, sex, needle size, number of attempted dural punctures, needle bevel direction, duration of postoperative recumbency, and previous PDPH was analyzed. Multivariate analysis showed that age (P < 0.0001), direction of the

bevel of the needle when puncturing the dura mater (P = 0.022), and a history of previous PDPH (P = 0.018) were significant predictors of PDPH. The estimated relation between PDPH, on the one hand, and age and orientation of the bevel, on the other, enables the anesthetist to predict the risk of PDPH and thereby to choose an acceptable age limit for spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—headache. COMPLICATIONS, POSTDURAL PUNCTURE HEADACHE.

Postdural puncture headache (PDPH) is a wellknown complication in procedures in which the dura mater is perforated, including spinal anesthesia and epidural anesthesia with accidental dural puncture. The following factors are thought to influence the incidence of PDPH: (a) age-higher incidence in younger patients (1-11); (b) gender—higher incidence in females (3-5,8-14); (c) needle size-the larger the diameter of the needle, the higher the incidence and the more prolonged and severe the PDPH (1,3,4,6–15); (d) multiple dural punctures higher incidence associated with increased number of perforations of the dura mater (16); (e) needle bevel direction and relationship to dural fibers—higher incidence if the needle is inserted perpendicularly to the longitudinal dural fibers, thus cutting them instead of separating them (9,17-20); (f) duration of postoperative recumbency—conflicting results indicate questionable relevance of this factor on the incidence of PDPH (11,21-27); and (g) previous history of PDPH—higher incidence in this group (11,26).

The purpose of the present prospective study was to investigate the influence of the above factors on the incidence of PDPH in a series of consecutive patients, during a period of 1 yr.

Patients and Methods

The study was approved by the local ethical committee and informed consent was obtained from each patient. Noncooperative patients and patients with senile dementia or migraine were not included in the study.

During a period of 1 yr 1021 spinal anesthesias for different types of surgery below the diaphragm were performed in 873 patients at the Central Hospital of Esbjerg. Multivariate relationships were analyzed using the hierarchical log-linear methods applying the backward elimination principle. A P value of <0.05 was considered statistically significant.

Anesthetic Technique

Premedication consisted of 1.25–2.5 mg of oral lorazepam about 1 h before the operation. All patients were hydrated with at least 0.5 L of intravenous crystalloid solution unless specific contraindications were present. The lumbar puncture was performed

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through a suitable interspace (L2-3, L3-4, or L4-5) with the patient in the sitting or lateral decubitus position. The patients were instructed to remain maximally flexed and not to move their heads during the needle insertion. An assistant helped them maintain this position. A standardized technique was used with the variables of age, sex, lumbar puncture needle size, number of attempted punctures, needle bevel direction (insertion perpendicular or parallel to the longitudinal dural fibers), and position of the patients during lumbar puncture (sitting or lateral decubitus position) recorded.

Having established free flow of cerebrospinal fluid (CSF) through the needle, 2.5–4.5 mL of one of the routinely used local anesthetic solutions (0.5% bupivacaine with or without glucose, 0.5% tetracaine with glucose, or 5.0% lidocaine) was injected. Hypotension was treated with volume expansion and elevation of the patients' legs and, if indicated, a vasopressor (5 mg ephedrine) was given intravenously. Intraoperative sedation was achieved with incremental intravenous doses of midazolam on the patients' request.

Procedure

The patients' electrocardiogram, pulse rate, and blood pressure were monitored and recorded throughout the procedure. Further levels of anesthesia, as determined by pinprick, onset time of adequate levels of surgical anesthesia, duration of the surgical procedure, details of the anesthetic administration, and sequelae during the first 2 wk postoperatively were recorded.

All patients were inpatients. After surgery the patients stayed in bed until somatic motor paralysis had completely regressed. They were allowed to stand thereafter if the surgery permitted. A questionnaire concerning PDPH was completed on the first postoperative day by each patient and an interviewer. The duration of the postoperative recumbency in bed was recorded. Patients were informed about the typical characteristics of PDPH and were asked to complete two additional questionnaires concerning PDPH, one before leaving the hospital and the other within 2 wk after the operation. Patients who did not return questionnaires were excluded from the study. All patients who complained of headache-including PDPH-were contacted by the same investigator who then recorded the type, severity, and duration of the headache.

A headache was considered as being a typical PDPH if it fulfilled the criteria laid down by Driessen

Table 1. Physical and Demographic Characteristics

	Median	Range	Number (%)	
Age (yr)				
Males	57	1 6-9 0	593 (67.9)	
Females	52	15-93	280 (32.1)	
Weight (kg)	74	38-125		
Height (cm)	173	145-203		

et al. (10), i.e.: (a) the headache occurred typically after the patient became ambulatory, was aggravated in the errect or sitting position, and was relieved by the patient's lying flat; (b) the localization was mostly occipital or frontal; and (c) the headache was accompanied by dizziness, vomiting, rigidity of the neck, and visual or auditory disturbances.

Postdural puncture headache, when present, was treated with bed rest, hydration, and oral analgesics for a few days and thereafter, if headache persisted, the patient was offered an epidural blood patch.

Results

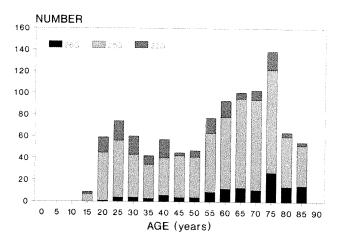
A total of 873 patients were given 1021 spinal anesthesias (593 males and 280 females given 722 and 299 anesthesias, respectively). The patients' age, sex, weight, and height are presented in Table 1. The ASA physical status was I in 674, II in 256, and III in 91.

These 873 patients constituted 87% of all eligible patients given spinal anesthesia during 1 yr. An additional 65 patients (6%) were not included in the study because their physical status was classified as ASA IV–V, or because they did not want to participate, and a further 77 patients (7%) were not included because they failed to return their questionnaires.

The distribution of patients by age is shown in Figure 1. The spinal anesthesias were given for orthopedic (n = 595) or genitourinary (n = 426) surgery by 10 anesthetists. Of the 1021 spinal anesthesias, 122 (11.9%) were complicated by headache postoperatively. Seventy-five patients (7.3% of the overall sample) had typical PDPH according to the criteria of Driessen et al. (10).

The multivariate association between the frequency of PDPH, on the one hand, and the number of punctures, size of the needle (22 gauge [n=127], 25 gauge [n=745], or 26 gauge [n=149]), sex, position of the patient during introduction of the needle (sitting/lying), direction of the needle bevel, and age, on the other hand, was analyzed.

The frequency of PDPH, statistically significantly but inversely associated with age (P < 0.0001), was



<u>Figure 1</u>. Distribution of spinal anesthetics in different age groups in relation to gauge of the needle used.

<u>Table 2</u>. Multivariate Relationship Between Postdural Puncture Headache and Pre-, Peri-, and Postoperative Factors

Factor	P value ^a		
Age	< 0.0001	S	
Direction of the bevel of the needle	0.022	S	
Previous PDPH	0.0018	S	
Gender	0.118	NS	
Size of the needle	0.105	NS	
Multiple perforations	0.091	NS	
Position of the patient at the time of lumbar puncture	0.192	NS	
Duration of postoperative recumbency	0.650	NS	

NS, not significant; S, significant; PDPH, postdural puncture headache.
^aP value before exclusion during backward elimination in the hierarchical log-linear model.

also significantly related to the direction of the bevel during introduction of the needle (P=0.022) (Table 2). No statistically significant association was found between PDPH and number of punctures (P=0.091), size of the needle (P=0.105), sex (P=0.118), or position of the patient at the time of lumbar puncture (P=0.192) (Table 2). No significant interaction was found between direction of the needle bevel and age (P=0.93), and no second-order interaction was found between the incidence of PDPH, direction of the bevel during the introduction of the needle, and age (P=0.37).

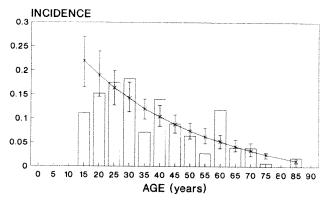
Information about the duration of recumbency after the anesthesia was available in 526 cases. Multivariate analysis of the relationship between PDPH, age, direction of the bevel during the introduction of the needle, and duration of recumbency was carried out in these 526 patients. The duration of recumbency was dichotomized into short (<4 h [47%]) and long (>4 h). The frequency of PDPH was not significantly

<u>Table 3</u>. Direction of the Bevel of the Spinal Needle in Relation to the Longitudinal Dural Fibers

	PDPH	
	Yes	No
Perpendicular	51	499
Parallel	24	436

PDPH, postdural puncture headache.

Data on needle direction were missing in 11 cases without headache. Relative risk = 1.78, confidence limits = 1.1-2.9, P = 0.02.

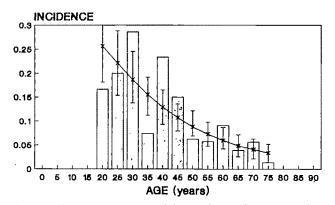


<u>Figure 2</u>. Logistic regression of the incidence of PDPH as a function of age (n = 1021): Pa = $[1 + \exp(0.633 + 0.039 \times \text{Age})]^{-1}$, 95% confidence limits are indicated by *solid lines* and the proportion of PDPH in each age group is indicated by *bars*.

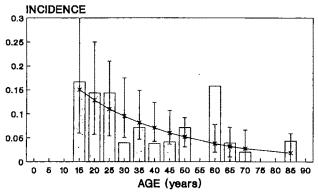
related to the duration of recumbency (P = 0.65), but a significant relation between duration of recumbency and age was found (P = 0.012).

The 117 anesthesias in which the patients had had a spinal anesthesia before were subjected to multivariate analysis of the relationship between PDPH, age, direction of the bevel during introduction of the needle, and previous PDPH. Previous PDPH was found to be a significant predictor of PDPH (P = 0.0018). In these 117 anesthesias PDPH developed in five cases; two in three subjects with a previous PDPH and three in 114 subjects without a previous PDPH.

In Table 3 the incidence of PDPH is given as a function of the direction of the bevel of the spinal needle. The incidence of PDPH among patients in whom the bevel was inserted parallel to the longitudinal dural fibers was 0.56 times the incidence among patients in whom the bevel was inserted perpendiculary to the longitudinal dural fibers. The association between PDPH and age (Pa), with the bevel of the needle inserted parallel (Ppa) or perpendicular (Ppp) to the longitudinal dural fibers, was assessed by logistic regressions. Figures 2–5 illustrate the resulting equations:



<u>Figure 3</u>. Logistic regression of the incidence of PDPH as a function of age and position of the bevel of the needle (perpendicular to longitudinal dural fibers) (n = 550). Ppa = $[1 + \exp{(1.303 + 0.032 \times Age)}]^{-1}$. 95% confidence limits are indicated by *solid lines* and the proportion of PDPH in each age group is indicated by *bars*.



<u>Figure 4</u>. Logistic regression of the incidence of PDPH as a function of age and insertion of the bevel of the needle (parallel to longitudinal dural fibers) (n = 460). Ppp = $[1 + \exp(0.224 + 0.043 \times \text{Age})]^{-1}$. 95% confidence limits are indicated by *solid lines* and the proportion of PDPH in each age group is indicated by *bars*.

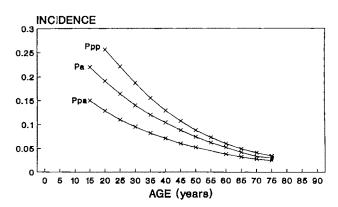
$$Pa = \frac{1}{[1 + \exp(0.633 + 0.039 \times Age)]},$$

$$Ppa = \frac{1}{[1 + \exp(1.303 + 0.032 \times Age)]},$$

$$Ppp = \frac{1}{[1 + \exp(0.224 + 0.043 \times Age)]}.$$

Discussion

The most widely accepted theory concerning the cause of PDPH is based on the concept of loss of CSF through a dural tear. When the patient assumes an upright position the brain is thus deprived of its cushion with increasing tension being exerted on anchoring structures innervated with stretch-sensitive fibers. The lumbar CSF fluid pressure normally increases from 5 to 15 cm $\rm H_2O$ in the horizontal position to about 40 cm $\rm H_2O$ in the sitting position (28). Owing to the pressure gradient between the



<u>Figure 5</u>. Logistic regression of PDPH as a function of age (Pa) and parallel (Ppa) or perpendicular (Ppp) insertion of the bevel of the needle in relation to the longitudinal dural fibers.

intradural and extradural space, spinal fluid is lost into the epidural space as long as the hole in the dura mater exists. The amount of fluid lost is dependent on the size of the hole and the rate of the CSF production. Withdrawal of CSF in the sitting position and onset of headache has been demonstrated in volunteers (29). Replacement of the withdrawn CSF with saline, using a volume of saline equal to the volume of CSF withdrawn, relieves the headache (29).

Many investigators have shown PDPH to be more common in young patients than in older ones (1–11). We observed the same relationship and have constructed mathematical equations illustrating the relationship between incidence of PDPH and age to predict the risk of PDPH (Figures 2–5).

It is generally believed that gender also plays a role in the occurrence of PDPH (3–5,8–14). We did not, however, find a significant association between gender and incidence of PDPH. The often quoted retrospective study of nearly 11,000 spinal anesthetics by Vandam and Dripps (4) found female patients to be twice as susceptible to PDPH as males (14% vs. 7%). However, in their study only bivariate analysis was carried out, and the positive association between PDPH and female sex may be due to a generally lower age and the inclusion of obstetric cases in the female group. None of our female patients were obstetric patients.

The leakage of CSF through a tear in the dura mater can be effectively diminished by the use of small-gauge needles. As early as in 1926 Greene (30) demonstrated that puncture with a 19-gauge needle was followed by greater CSF loss than puncture with a 22-gauge needle. A reduction in the incidence of PDPH from 14% to 6% was observed by Vandam and Dripps (4) when a 24-gauge spinal needle was used instead of a 20-gauge needle. Use of 29- and even

32-gauge needles has also been advocated (15). However, the technical problems associated with the use of very fine needles may lead to a decrease in the rate of successful spinal anesthetics. In our study, however, we did not observe any statistically significant association between needle gauge in the range 22, 25, and 26 gauge and the incidence of PDPH.

It has been shown that PDPH is more common if two verified punctures into the subarachnoid space are made (16) but the present study showed no statistically significant association between PDPH and number of attempted dural punctures. The way the dura mater was punctured proved to be a more important factor in our study. The incidence of PDPH was thus nearly doubled when the bevel of the needle was inserted perpendicularly instead of parallel to the longitudinal dural fibers, thereby presumably cutting the fibers instead of separating them (Figures 3-5). Dittmann et al. (31) investigated the effects of spinal puncture with 20-, 22-, 26-, and 29-gauge needles in a study of five fresh cadavers. They found that the most important factor determining the size of the hole to be the size of the needle. The size and shape of the hole depended to a lesser degree on the direction of the needle bevel. They also found that the texture of the dura mater and especially the arrangement of the elastic fibers are not uniform, as stated in earlier reports (17,30,32).

Our results agree with those of Mihic (17), who also found the direction of the bevel of the needle puncturing the dura mater to be a more important determinant of the occurrence of PDPH than needle size (22- vs 25-gauge needles), age, sex, or duration of postoperative recumbency. Further, it was shown that, when the bevel was parallel to dural fibers during perforation of the dura mater, there was no significant difference between 22- and 25-gauge needles with regard to the incidence of PDPH (17). This suggests that use of 26-gauge or even smaller sizes may not be relevant with respect to reduction of the incidence of PDPH.

It has been assumed in the past that sufficiently long postoperative recumbency prevents or reduces the incidence of PDPH. Several controlled trials have, however, shown that the duration of the recumbency after lumbar puncture has no effect on the incidence of PDPH (11,22–27). Thornberry and Thomas (27) even recommend early mobilization to prevent PDPH after obstetric procedures under spinal anesthesia. Our study demonstrated that there was no relation between the time spent recumbent after spinal anesthesia and the occurrence of PDPH. The only reason for prophylactic recumbency should be to prevent

hypotension, as sympathetic blocks last longer than somatic motor and sensory blocks.

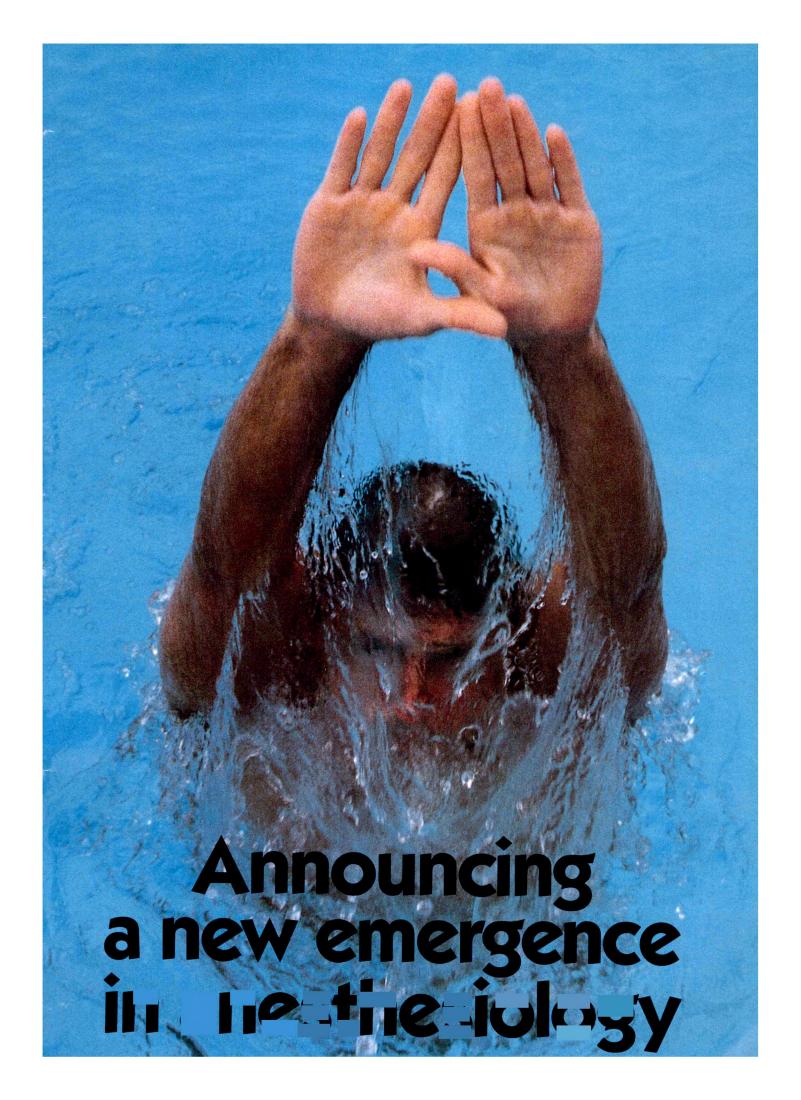
In conclusion, we found that it is possible to predict outcome in respect to morbidity after spinal anesthesia as the risk of PDPH can be estimated from the age of the patient and the bevel direction of the spinal needle.

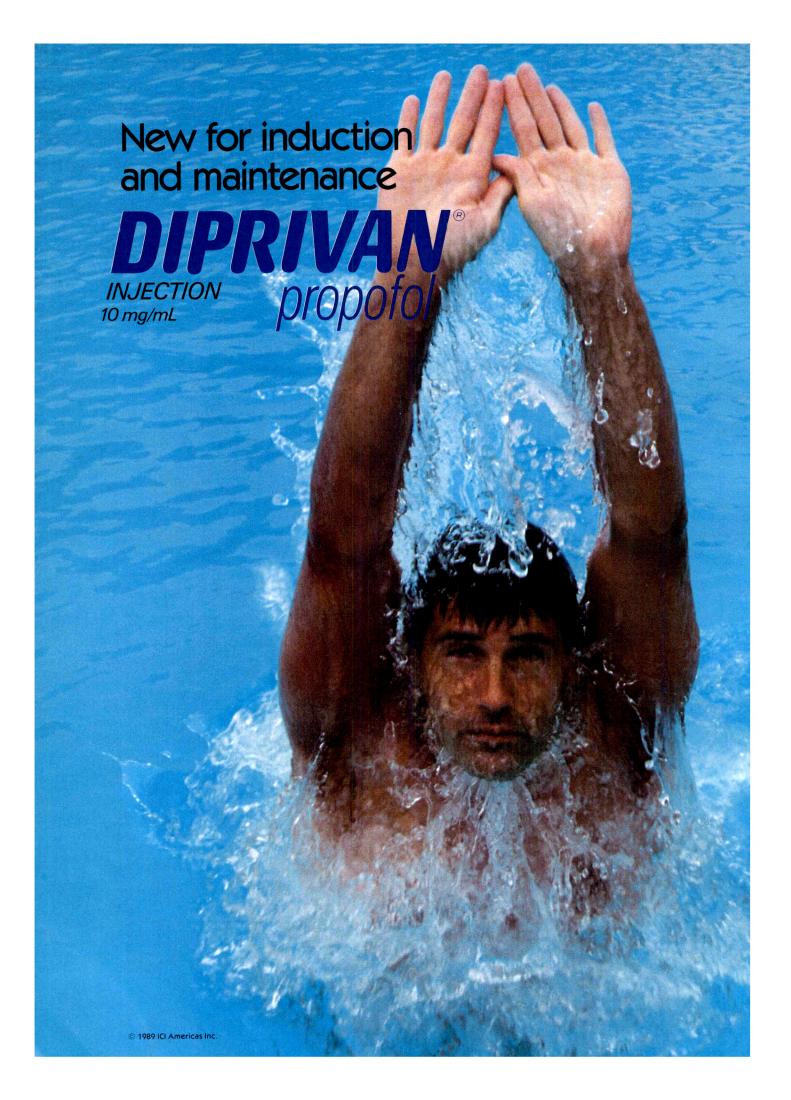
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The first of a new class of IV anesthetic agents for induction and maintenance

DIPRIVAN, an alkylphenol, provides:

Rapid, predictable onset

 smooth induction with minimal excitation (one arm-brain circulation)

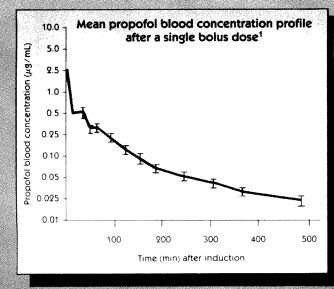
Rapid metabolism and extensive distribution*

- total body clearance exceeds estimates of hepatic blood flow¹
- no active metabolites

Rapid, clearheaded awakening

- majority of patients are generally awake, responsive, and oriented within 8 minutes
- low incidence of nausea and vomiting²

^{*}As with most anesthetic agents, the clearance rate of DIPRIVAN decreases in elderly patients.



DIPRIVAN clearance 5-10 times faster than barbiturates Clearance rate (L/min) ¹					
DIPRIVAN	1.6-3.4				
thiopental ³	.1130				
methohexital ³	.7084				

¹Calculations of clearance rates based on 70-kg patient —adapted from Way and Trevor, p 803³

Alexander and

Significantly Taster recovery profile

Awakening that faster with DIPRIVAN than with this pental considerable higher for discharge significantly

Mean postanesthesia recovery times (mi		
		223
	医最级	238
	M. F 200	

	DIPRIVAN	Thiopental/isoflurane	
Duration of anesthesia	85*	57	
Response to commands	3.5*	6.1	
Eyes open spontaneously	4.0*	6.3	
Fully oriented	5.5	9.4	
Able to tolerate fluids	61*	130	
Able to stand unassisted	68	87	
Able to walk unassisted	70	0 96	
Able to void	102*	173	
"Ready" for home	138*	206	

^{*}Statistically significant (P < 0.05).

Measurements taken from time of discontinuation of all maintenance anesthesia

With less of the nausea and vomiting assectional with other anesthetic agents—up to 24 hours posted



Superior recovery

Improved speed and quality of recovery compared with thiopental/isoflurane:

more rapid time to extubation⁵
more rapid and clearheaded awakening⁶⁻⁸
lower incidence of nausea and vomiting^{2,7}
patients able to tolerate fluids faster^{2,4}

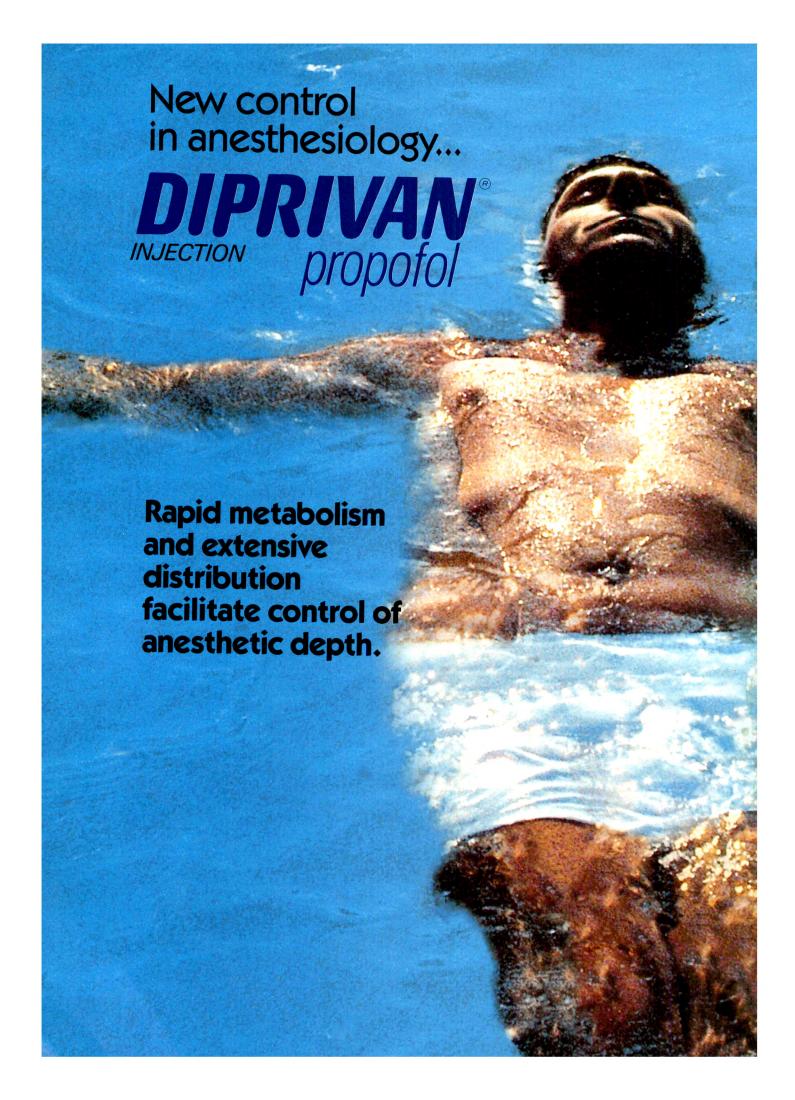
Earlier discharge from PARR*

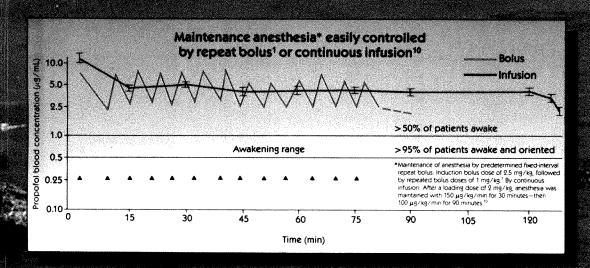
more efficient utilization of OR/PARR facilities⁹ increased nursing efficiency⁹ rapid return to routine self-care activities

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

*An adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia.







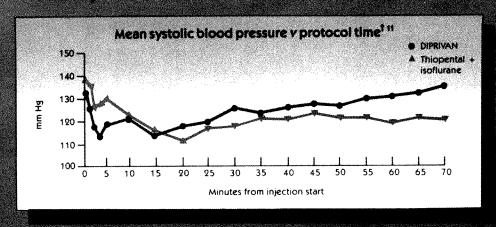
Assessment of maintenance*11

E	xcellent	Good	Poor
DIPRIVAN (n = 50)	58%	30%	12%
Thiopental + isoflurane (n = 50)	36%	32%	32%

^{*}Statistically significant differences between all treatment groups (P < 0.05, Mantel-Haenszel Test)—as measured by the percent variation from baseline in hemodynamic parameters.

Worldwide expression in over 7 (COM) to the tenter.

- Eficiosoppinks Sijes stadingins etter oceasgeristelijk more oromannese über with breedit oceil Windelieden Krista
- Blood pressure predictats hydratic legics on industrial (sometimes > 30%) but was within acceptable tanges for realthy individuals.*



Increase in heart rate following intubation was less pronounced than after thiopental with isoflurane. 11,12

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.*

In clinical trials including over 1500 DIPRIVAN patients, most adverse events were mild and transient

Transient local pain (≥10%) may occur during IV injection; venous sequelae have rarely been reported (<1%).

Apnea often occurs on induction (43%) and may persist for more than 60 seconds.

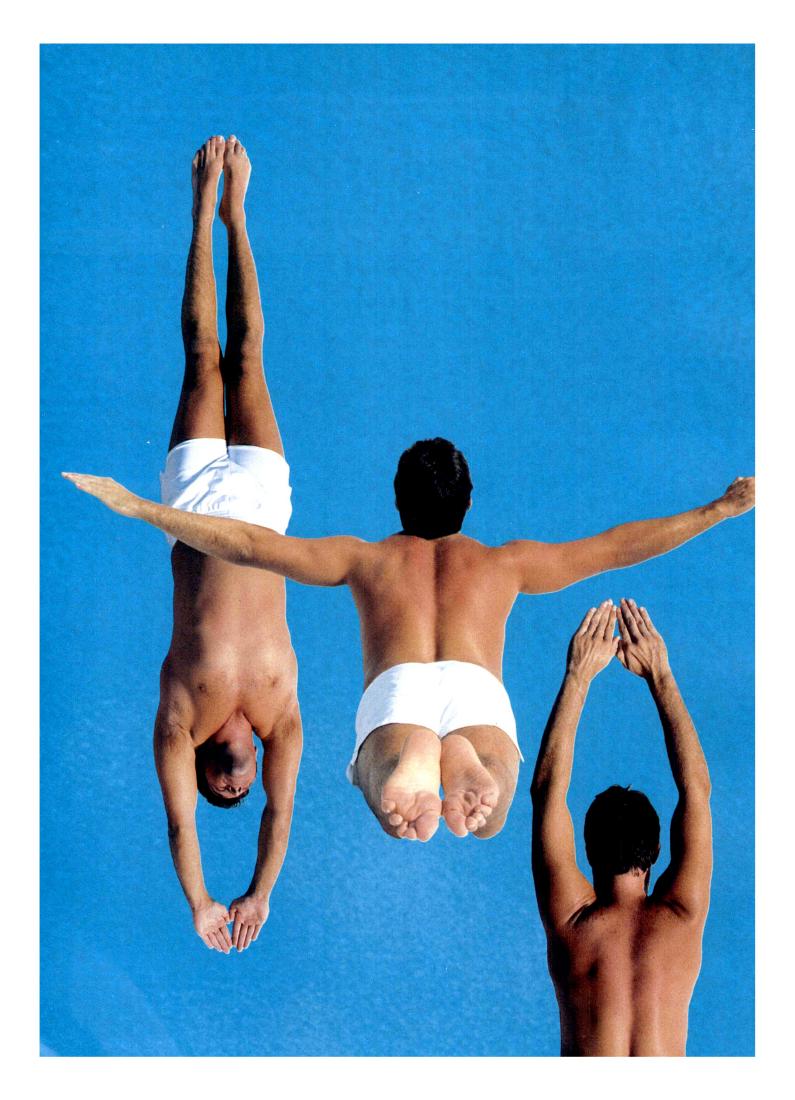
Significant hypotension (5.5%) and bradycardia (2.4%) have been reported[†]; experience has shown them to be clinically manageable.

Low overall incidence of nausea (16.7%) and vomiting (9.1%).

*Induction dose requirements may be reduced.

[†]Sufficient to require intervention.





New versatility in anesthesiology...



For a wide variety of procedures... outpatient and inpatient

- Gynecologic
- Urologic
- Ophthalmic

- Orthopedic
- Dermatologic
- Diagnostic

■ ENT

■ General surgery

DIPRIVAN should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

DIPRIVAN should be used with caution in elderly, debilitated, and/or hypovolemic patients, and those rated ASA Class III or IV.

DIPRIVAN is not recommended at this time for use in pediatric patients, nursing mothers, patients with increased intracranial pressure or impaired cerebral circulation, and in obstetrics, including cesarean section deliveries.

- DIPRIVAN can be combined with other commonly used agents in anesthesia.
- Also eliminates concerns about operating room/ recovery room pollution associated with volatile agents.

For induction and maintenance...

DIPRIVAN®

INJECTION 10 mg/mL propofol

The new IV anesthetic agent with a unique pharmacokinetic profile

- for rapid, predictable onset of anesthesia
- for smooth induction with minimal excitation
- for easily controlled maintenance of anesthesia
- for rapid, clearheaded awakening—with a low incidence of nausea and vomiting

Extensive worldwide experience

in a wide variety of surgical procedures outpatient and inpatient

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

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DIPRIVAN° INJECTION Propofol

EMULSION FOR IV ADMINISTRATION

DESCRIPTION: DIPRIVAN® (proporol) injection is a startle, nonpyrogenic amulsion containing 10 mg/mL of proporol suitable for intravenous administration. Proporol is chemically described as 2.6-Dilsopropylphenol and has a molecular weight of 178.27. The empirical and structural formulas are:

Proposol is very slightly soluble in water and, thus, is formulated in a white, cli-th-water emulation. The emulation is isotonic and has a pH of 720-85. In addition to the active component, proposol, the formulation also contains sopbean oil (100 mg/mL), glycerol (22.5 mg/mL) and egg lacithin (12 mg/mL); with sodium hydrodie to adjust pH. CLBICAL PHARMARCOLOGY. DIPRIVAN injection is an intravenous hyporobic agent for use in the induction and maintenance of anesthesia. The pharmacokinetic profile of DIPRIVAN injection can be characteristed sollows: After a single rapid IV boilus dose, two distribution phases are seen, a rapid phase with a half-life of 1.9 to 8.3 min and a slower phase of 34 to 64 min. These distribution phases are associated with the movement of DIPRIVAN from highly perfused tissues (Vessel-Hot tissues) to be asse well-perfused tissues the terminate inhalf-life of DIPRIVAN ranges from 500 to 700 min. With protonged administration of DIPRIVAN injection, the terminal estimation half-life may become extended beyond 700 min. DIPRIVAN has a high metabolic clearance exceede estimation in healthy 70 kg patients. This metabolic clearance exceede estimation half-life of DIPRIVAN in suggesting poserible extrahepatic metabolism. DIPRIVAN has a large steady state distribution volume that ranges from 150 to 1,000 liters in healthy 70 kg patients. The long terminal estimation half-life of DIPRIVAN is due to the large steady state distribution volume which is presumed to be due to extensive drug partitioning into tissues.

The termination of anasthetic drup effects of DIPRIVAN after a single IV bolus or a maintenance infusion is The termination of anesthetic drug effects of DPFRIVAN after a shaple IV bolus or a maintenance influsion is due to extensive redistribution from the CNS to other tissues and high metabolic clearance both which will decrease blood concentrations. Recovery from anesthesia is rapid. Following induction (2.0 to 2.5 mg/kg DPRIVAN injection) and maintenance (0.1 to 0.2 mg/kg/min) of anesthesia for periods up to two hours, the majority of patients are generally evaller, responsive to verbal commands, and oriented within 8 minutes. Recovery from the effects of DPRIVAN injection occurs due to metabolism and distribution during the first two exponents of the decay curve and is not dependent on the terminal elimination half-life. A study in six subjects showed approximately 70% of the administrator gradieded DIPRIVAN injection dose was recovered in the urrise in the six 4.4 hours and approximately 90% of the dose was recovered in the urrise within five days. DIPRIVAN is chiefly metabolized by conjugation in the liver to inactive metabolites which are excreted by the kidney. A glucuroride conjugation matabolite accounted for about 50% of the administrate dose, it he each metabolic fate of DIPRIVAN and the effect of possible distribution and the effect of possible distributions.

contingation matabolite accounted for about 50% of the administered dose. The exact metabolic tate of DPHWAN and the sites of possible "extrahepatic" metabolism have not been lidentified.

The pharmacokinetics of DPHMAN Injection do not appear to be attered by gender, chronic hepatic cirrhosis or chronic renal failure. The effects of acuts hepatic or renal failure on the pharmacokinetics of DIPHMAN have not been studied. With increasing age the clearance of DIPHMAN decreases from a mean ± 5.0. of 1.8 ± 0.0. to 1.4 ± 0.4 L/min in editorly (65-80 years) patients. When given by an infusion for up to two hours, the pharmacokinetics of DIPHMAN appear to be independent of dose (0.05-0.15 mg/kg/min) and similar to IV boths pharmacokinetics. The steady state propositioned concentrations are improved to the proposition of the order of the proposition of the proposi

mg/lg/min) and similar to IV botus pharmacokinetics. The steady state proportion to the rate of administration. Other drugs that cause ONS depression (hypnotics/sedatives, inhalational anesthetics and nercotics) can increase the CNS depression induced by DPRIVAN. Morphine premedication (0.15 mg/lg) with N₂O 67% has been shown to decrease the necessary DIPRIVAN injection maintenance infusion rate and therapeutic blood concentrations, when compared to a nonnarrootic (lorazepum) premedication. An afantant limitation rate of 50 ag/lg/h has been shown to replace the anesthetic effects of N₂O 67% and morphine premedication. Intravenous injection of a therapeutic close of DPRIVAN injection produces hypnosis rapidly and morphine with minimal exclusion, usually within 40 seconds from the start of an injection (one arm-brain circulation time). As with other rapidly acting intravenous anesthetic agents, the half-time of blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

Percordio flooring recognitions required for maintenance of anesthesia have not been completely observed.

approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

Propotol blood concentrations required for maintenance of anesthesia have not been completely characterized.

When nitrous codds, oxygen, and propotol are used for maintenance of general anesthesia, supplementation with analyseic agents (e.g., narcotice) is generally required; neuromuscular blocking agents may also be required.

(See DOSAGE AND ADMINISTRATION.)

The hemodynamic effects of DPFIVAN injection during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease) with fittle or no change in heart rate and no eppreciable decrease in cardiac output. If will altitude is assisted and controlled (opidite pressure vertiliation), the degree and incidence of decrease in cardiac output are accentuated. Addition of a potent opioid (eg., fentanyl) when used as a premedicunt further decreases cardiac output. If anesthesia is continued by Infusion of DPPRAN injection, endotrached inhubetion and surgical stimulation may are not decreased. Comparative clinical

may return arterial pressure towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of DIPRIVAN during induction are generally more pronounced

studies have shown that the hemodynamic effects of DIPHIVAN during induction are generally more pronounced than with traditional IV induction agents.

Insufficient data are evaluate regarding the cardiovascular effects of DIPHIVAN injection when used for induction and/or maintenance of anesthesis in extenty, hypoxolemic, hypotensive, debilitated patients, patients with severa cardiac disease (ejection fraction < 50%) or other ASA BUTV patients. However, limited information suggests that these patients may have more profound adverse cardiovascular responses. It is recommended that if DIPHIVAN injection is used in these patients, a tower induction dose and a slower maintenance rate of administration of the drug be used. (See DOSAGE AND ADMINISTRATION.)

Clinical and preclinical studies suggest that DIPHIVAN injection is rarely associated with elevation of plasma histoamine levels and dose not cause signs of interarrier release.

instrainmentees and coes not cause signs or installant research. Induction of anesthesia with DEPRIVAN injection is frequently associated with apnea. In 1573 patients who received DEPRIVAN injection (2.0 to 2.5 mg/kg), apnea lasted 0-30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. During maintenance DEPRIVAN injection to 0.2 mg/kg/mm) causes a decrease in vertication and with an increase in carbon disolde tension which may be marked depending upon the rate of administration and other concurrent medications (eg. narcotics,

ed arrives, etc.). Clinical studies in humans and studies in animals show that DPRIVAN injection does not suppress the adrenat

response to ACTH.

Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN injection anesthesia produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic verscular registance.

Animal studies and limited experience in susceptible patients have not indicated any prope

Injection to Induce malignant hyperthermia.

BIDICATIONS AND URAGE: DIPRIVAN Injection is an IV anasthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN injection is not recommended for obstatrics, including osamean section deliveries, because there are insufficient data to support its safety to the lettus. (See PRECAUTIONS.)

DIPRIVAN hybotion is not recommended for use in nursing mothers because DIPRIVAN injection has been

reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommanded for use in pediatric patients because safety and effectiveness have

DIPRIVANº (prepotol) kajection

not been established. (See PRECAUTIONS.)

DEPRIVAN Injection is not recommended for use at this time in patients with increased intracrantal pressure or impaired carebral circulation because DEPRIVAN injection may cause substantial decreases in mean arterful pressure, and consequently, substantial decreases in cerebral perhasion pressure. (See PRECAUTIONS.)

CONTRAMADICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity

CORT INNERVAND injection or the components are scalars as a contraint case or in patients with a now in passessivity to DPRIVAN injection should be administrated only by persons trained in the administration of general anesthesis. Positifies for maintenance of a person anesthesis. Positifies for maintenance of a person anesthesis. Positifies for maintenance of a person anesthesis. Positifies for maintenance and circulatory mesonicitation most be immediately available.

DIPRIVAN injection should not be condiministered through the same fV catheter with blood or plasma because

compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the amulsion vehicle have occurred with blood/plasma/sarum from humans and animals. The clinical simificance is not known

significance is not known.

PRECALITIONS: General: A lower induction dose and a slower maintenance rate of sommistration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or M. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously mentored for early signs of significant hypotension and/or breatycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower externitions. use of pressor agents, or administration of atrophie, Apines often occurs during induction and may pensist for more than 60 seconds. Ventilatory support may be required. Because DIPRANAI Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic

hyperlipemia, and pancreatitis.

Since DIPRIVAN injection is never used alone, an adequate period of evaluation of the av Indicated to ensure satisfactory recovery from general enesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV Idocaine (1.0 mL of a 196 solution). Venous sequeiae (phiebitis or thrombosis) have been reported rarely (< 196), in two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequeiae were reported controlled clirical studies using dedicated intravenous catheters, no instances of venous sequetae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecultrial feas are used. Accidental clinical extraversation and intertional injection into subcutaneous or pervisacular dissues of animals caused minimal tissue reaction, intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae. Perioperative myocionia, rarely including opistitionus, has occurred in a temporal relationship in cases in which DIPRIVAN injection has been admir/stered.

Rarely, a clinical syndrome which may ir clude bronchospasm and enythema accompanied by hypotension has occurred shortly after the administration of DPRIVAN injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN injection unclear.

Drug interractions: As DIPRIVAN injection has no vagolytic activity, premedication has usually included articloinencia carents (e.g. attronities or obscorvmental to modify potential locareasses in vasual tone due to

anticholinergic agents (eg. stroptne or glycopyrrotate) to modify potential increases in vagal tone due to concomitant agents (eg. succlay/choline) or surgical stimuti.

The induction dose requirements of DIFRIMAN injection may be reduced in patients with intramuscular or

The Induction dose requirements of DIFRIVAN Injection may be reduced in patients with intramuscular or intreserous premedication, particularly with narcotics (e.g. morphine, meperidine, and tentaryl) and combissions of narcotics and seatatives (e.g. benzoolazzepines, barbiturates, chioral hydrate, dropariod), etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, disastolic, and mean arterial pressures and cardiac output. During mainterance of anesthesis, the race of DIPRIVAN injection administration should be adjusted according to the desired level of enesthesia and may be reduced in the presence of supplemental analogistic agents (e.g., nitrous codes or opioids). The concurrent administration of potent inhalational agents (e.g., introus codes or opioids). The concurrent administration of potent inhalational agents (e.g., introus experiments). These planets.

and the course of outring maintenance with D PRIMAN injection has not been extensively evaluated. These inhala-tional agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIMAN injection. DIPRIMAN injection does not cause a chically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (e.g., succhystoniae and nondepolariting must effect relationships and configurations of actionships and promodulations or drugs used during anesthesia.

(including a range of muscle relevants, inhalational agents, analgesic agents, and local anesthetic agents) have een observed.

Carolinogenasis, Mutagenesis, Impelment of Fertility: Animal carcinogenicity studies have not been performed

with proportiol.
In vitro and in vivo animal tests failed to show any potential for mutagenicity by proportiol. Tests for mutagenicity included the Ames (using Saimonelle sp) mutation test, gene mutation/gene conversion using Saccharomyces corevisiae, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

cerevisies, in vitro cytogenetic studies in Cidnese hamsters and a mouse micronucleus test.

Studies in femate rats at intraverous does up to 16 mg/kg/dw (6 time of the maximum recommended human induction does) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertifity. Male fertifity in rats wes not affected in a dominant lettral study at intravenous doese up to 16 mg/kg/day for 5 days.

Pregsamey Catagery B: Reproduction studies have been performed in rats and rabbits at intravenous doese of 15 mg/kg/day (6 times the recommended human induction does) and have revealed no evidence of impaired fertifity or harm to the fetus due to proportol. Propoloi, however, has been shown to cause maternal deaths in rate and rabbits and decressed up up unrivaled ultring period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction does). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because mirral reproduction studies are not always predictive of human responses, the drug should be used during pregnancy only if clearly needed.

Labor and Bellwery: DPRANAN injection is not recommended for obstatrics, including cesarean section deliveries, hocause there are insufficient data to support its safety to the fatur.

Next lag Mothers: DIPRANAN injection is not recommended for use in nursing mothers because DPRINAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of proporol are not lowers.

Padiatric Usa: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

effectiveness have not been established.

Reumeargleat Anesthesia: Studies to date indicate that DIPRIVAN injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovescular resistance.

DIPRIVAN injection does not seem to affect cerebrovescular reactivity to changes in arterial carbon dicedite tension. Despite these findings, DIPRIVAN injection is not recommended for use at this time in patients with increased intracrantel pressure or impetred cerebral circulation because DIPRIVAN injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN injection when decreases in mean arterial and pressure continuing and pressure are necessarily and any appropriate pressures are necessarily as any provided and pressure successive and pressure are necessarily as any provided and pressure and pressure are necessarily as any provided and pressure and pressure are necessarily as any provided and pressure Further studies are needed to substantiate what happens to intracrunial pressure following IDPRIVAN injection when decreases in mean arbertal and central perfusion pressures are prevented by appropriate measures. ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marksting experience. In the description below, rates of the more common events represent US/Canedian circuit study results. Less frequent US/Canedian circuit study results. Less frequent vents are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for IDPRIVAN injection are derived from reports of 1673 patients included in the US/Canedian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were man text in preferred treated with DEPRIVAN injection. They are prepared to

The following adverse events were reported in patients treated with DIPRIVAN injection. They are present

The following adverse events were reported in patients treated with DPHNNAN injection. They are presented within each body system in order of decreasing frequency. Incidence Breather than 194—All events repartiess of caesality, served from citatest trials. Body as a Whatler Fever. Cardiovasceriar Hypotension' (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypotension. Caestral Reviews. Systems: Movement, "Heacache, Dezimess, Twitching, Bucking/Jerking/ Thrashing, Clonic/Myocionic Movement. Dispestive: Nausea," Verniting," Abdominal Cramping, larjection Sile: Burning/Sitinging," Pain," "lingifing/Numbness, Cotiness, Respiratory: Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). Shin and Appendages: Flushing. Incidence of unmarked events is 194-396. "396 to 1096; ""1096 or greated. Incidence Less tiken 194—Causel Relationship Probable (Adverse events reported only in the literature, not seen in citated trials, are Associated.)

seen in clinical trials, are kalicized.)

Body as a Whele: Extremitles Pain, Chest Pain, Neck Stiffness, Trunk Pain. Cardiovascular: Tachycardia, Premature Ventricular Contractions, Premature Artial Contractions, Syncope, Abnormal ECG, ST Segment Depression. Central Nerveus System: Shivering, Somnolence, Hypertonia/Dystonia, Parasthesia, Teropa Abnormal Dreams, Agitation, Confusion, Delirum, Eupharia, Fatique, Moening, Highlin, Digestive: Hypersalvation, Dry Mouth, Swallowing, Injaction Site: Discomfort, Philettile, Hivestitisting, Redness/Discoloration. Musculoskeletal: Myaigia. Respiratory: Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. Skin and Appendages: Rash, Urticaria. Special Senses: Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. Urogenital: Urine

Incidence Less than 1%— Causal Relationship Unknown (Adverse events reported only in the literature, not

seen in clinical trials, are *italicized.)*Cardiovascular: Arthythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, Myocardial Ischemia. Central Nervous System: Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures. Opisthotonus. Digestive: Diarrhea. Respiratory: Laryngospasm. Skin and Appendages: Diaphoresis, Pruritus, Conjunctival Hyperemia. Special Senses: Ear Pain, Nystagmus. Urogenital: Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of

should be freated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents.

The intravenous LD₅₀ values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA fand II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction, DIPRIVAN Injection should be titrated with oral benzolazegines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated to the patient until the clinical signs show the (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection, therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE). Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent. If hot patients can be maintained by administering DIPRIVAN Injection by infusion or intermittent.

IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps

or volumetric pumps be used to provide controlled influsion rates.

Continuous Influsion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate influsion with

60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%-50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are

not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie. intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory

nesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical simulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine,

scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. Adults: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	Variable rate infusion — titrated to the desired clinical effect. Adults: Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter -5% Dextrose Injection, USP

- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
 S% Dextrose and 0.45% Sodium Chloride Injection, USF

5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection should be discarded e surcical procedure

HOW SUPPLIED: DIPRIVAN Injection (NDC 0038-0290) is available in ready-to-use 20-mL ampules containing 10 mg/mL of propofel

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use

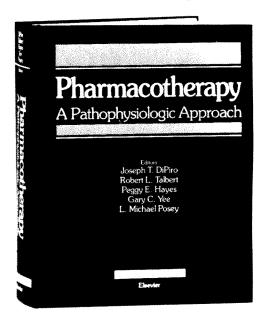
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RAPID ONSET AND



SMOOTH EMERGENCE GO HAND IN HAND

IN I.V. CONSCIOUS SEDATION

Rapid onset of sedation1

Minimal irritation and phlebitis after I.V. injection

 Only 1.29 percent (2/155) incidence of thrombophlebitis one week postprocedure with VERSED (midazolam HCI/Roche)²

Pronounced amnestic effect

 Minimal recall of the procedure – a majority of patients had little or no recall one hour postendoscopy.¹ Diminished recall is especially valuable when repeat procedures may be required.

Dosing Considerations

Because serious and life-threatening cardiorespiratory adverse events have been reported with VERSED, provide for monitoring, detection and correction of these reactions for every patient regardless of age or health status.

As a standard precaution, prior to I.V. administration, oxygen and resuscitative equipment should be immediately available and personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation should be ensured. I.V. VERSED should be titrated slowly; never give as a bolus. Respiratory depression and/or arrest may result from excess doses or rapid or single bolus. VERSED should be used as an induction agent only by persons trained in anesthesiology.

Reduce dosage in elderly or debilitated, in patients receiving narcotic premedication, and in those with limited pulmonary reserve. VERSED is 3 to 4 times as potent per mg as diazepam. Refer to the complete dosage and administration guidelines.

It is recommended that patients not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. Decision must be individualized.

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IN INDUCTION

Smooth emergence

 Patients treated with VERSED experience minimal anxiety and postoperative depression and rarely report any adverse emergence reactions.³

Better hemodynamic stability

 Less pronounced decreases in stroke volume, heart rate, cardiac output and systemic vascular resistance...and less pronounced increase in mean right atrial pressure compared to thiopental, although the differences were not statistically significant.¹



Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

Please see summary of product information on following page.

References: 1. Roche Scientific Summary: The Evaluation of VERSED® (brand of midazolam HCl/Roche) ©, Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, New Jersey, 1986 **2.** Phaosawasdi K, Rice P. SGA Journal:176-178. Spring, 1987 **3.** White PF. Anesthesiology 57:279-284, 1982

VERSED® (brand of midazolam HCI/Roche) (V

Before prescribing, please consult complete product information, a summary of which follows:

ntravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma, may be used in open angle glaucoma only if patients are receiving appropriate therapy WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken **immediately.** Vital signs should continue to be monitored during the recovery period Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only person relative in general artestiesta and should be used in Conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration, however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital

signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized, it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated

with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated

These patients will also probably take longer to recover completely after patients. These patients will also prof VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intub light general anesthesia.

Information for patients. Communicate the following information and instructions to the patient when appropriate 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital

VERSED* (brand of midazolam HCI/Roche) INJECTION

and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of

halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically signifi-cant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset of duration of a single intubating dose of succinylcholine. No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drugilaboratory test interactions: Midazolam has not been shown to interfere with

clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several

Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk

Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 years have not been established

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM injection: headache (1.3%), local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%), local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration. Respiratory: Laryngo-spasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. Gastrointestinal. Acid taste, excessive salivation, retching. CNS/Neuromuscular: Retrograde amnesia. euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. Integumentary: Hives, hive-like elevation at injection site, swelling of feeling of burning, warmth or coldness at injection site, rash, pruritus. Miscella-neous, Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma. Drug Abuse and Dependence Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equiv alent to that of diazepam

OVERDOSAGE: Manifestations would resemble those observed with other benzo-

diazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be

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Reversal of Bupivacaine Epidural Anesthesia by Intermittent Epidural Injections of Crystalloid Solutions

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JOHNSON MD, BURGER GA, MUSHLIN PS, ARTHUR GR, DATTA S. Reversal of bupivacaine epidural anesthesia by intermittent epidural injections of crystalloid solutions. Anesth Analg 1990;70:395–9.

This study was designed to determine whether epidural motor blockade could be reversed by postoperative injections of crystalloid solutions via the epidural catheter. Twenty-seven patients (ASA physical status I, nonlaboring) had epidural anesthesia with 0.75% bupivacaine for elective cesarean delivery. Postoperatively, patients were randomized to receive three 15-mL injections (over 30 min) of crystalloid solutions (normal saline or Ringer's lactate) or no treatment (control) via the epidural catheter. Degree of

motor and sensory blockade was evaluated with an investigator blinded to treatment group. Rate of resolution of sensory blockade was not different among groups. However, time for resolution of motor blockade was more than twice as long in the control group than in either treatment group (control = 178 ± 70 min vs Ringer's lactate = 84 ± 44 min, normal saline = 70 ± 38 min, P = 0.001). The data suggest that unwanted motor blockade due to epidural anesthesia can be reversed by epidural injections of crystalloid solutions.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—reversal. ANESTHETICS, LOCAL—bupivacaine.

Lumbar epidural anesthesia, when used for procedures such as cesarean delivery, occasionally results in prolonged postoperative motor blockade, contributing to patient anxiety and extended recovery-room stay. In such cases, it would be desirable to reverse or antagonize motor blockade. Local anesthetic-induced neuroblockade can be reversed rapidly by washing isolated nerve preparations with crystalloid solutions (1,2). For example, washing rat sciatic nerve preparations with Krebs-Ringer solution reverses bupivacaine-induced neural blockade in approximately 25 min (3). Thus, we designed a clinical study to determine if crystalloid solutions (Ringer's lactate [RL] or normal saline [NS]), injected into the epidural space at the termination of operation, could shorten the duration of motor blockade.

Methods

The study protocol was approved by our institutional committee for protection of human subjects. Written informed consent was obtained from 27 multiparous women (ASA physical status I) who were at term, not in labor, and wished to have epidural anesthesia for elective cesarean delivery. One patient was excluded from the study when, after induction of epidural anesthesia, the fetus converted from breech to vertex presentation and was delivered vaginally. Blood pressure was measured with an automated pressure cuff, and fetal heart rate was monitored via a transabdominal Doppler probe.

All patients received sodium bicitrate (30 mL orally), RL solution (1500 mL intravenously), and oxygen (6 L/min via face mask) before induction of anesthesia. An epidural catheter was placed via a 17-gauge Weiss needle at the L3-4 interspace, using a midline approach with the patient in the right lateral decubitus position. After advancing the catheter 2 cm caudad, the patient was positioned supine with 30° head-up elevation and left uterine displacement. After aspiration through the catheter was negative for blood or cerebrospinal fluid (CSF), epidural anesthesia was induced. Plain bupivacaine (0.75%) was in-

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jected, in 3-mL aliquots, every 3–5 min, until bilateral sensory anesthesia to T-6 or higher was achieved. Epinephrine-containing solutions were not used in this study. Blood pressure was maintained within 10% of baseline values with intravenous RL solution and/or intravenous ephedrine.

An investigator, blinded to treatment group (not present during epidural injections), measured the level of sensory anesthesia by pinprick and degree of motor blockade using the Bromage scale (4): inability to move toes, knees, or hips = 100% motor blockade; ability to move toes but not knees = 66% motor blockade; ability to move toes and partially move knees = 33% motor blockade; ability to fully move knees = no motor blockade. Levels of sensory anesthesia and motor blockade were recorded before abdominal incision, at the conclusion of operation, and at 15-min intervals during the recovery period. Time from the termination of operation to complete resolution of motor blockade was also recorded.

Patients were randomly assigned to one of three groups but were not informed of group assignment. In one group no crystalloid was injected epidurally (control), whereas the other two groups received 15-mL injections of RL or NS. Before each injection, aspiration of the catheter was negative for blood and CSF. The first injection was at the conclusion of operation; the next, 15 min after operation; and the final injection, 30 min after operation. At corresponding times in the control group, an anesthetist standing behind the patient shammed injections by manipulating the catheter. Catheters were removed in the recovery room at the conclusion of the 45-min study period. Epidural narcotics were not used.

Maternal plasma bupivacaine levels were determined in 20 patients (the others did not consent to this aspect of the protocol). Maternal venous samples were drawn at the conclusion of operation and 45 min later. Samples in groups receiving epidural injections were drawn immediately before the first injection (conclusion of operation) and 15 min after the final injection (45 min after conclusion of operation). Samples were centrifuged and supernatant fractions (plasma) were frozen at -20°C; plasma was subsequently assayed for bupivacaine according to the method of Tucker (5).

Data are expressed as mean \pm standard deviation unless otherwise indicated. Parametric comparisons were made via one-way analysis of variance, using Dunnett's test to contrast means. Nonparametric comparisons were made according to the Kruskal–Wallis test. A value of P < 0.05 was considered statistically significant.

Table 1. Demographics

Group	n	Age (ут)	Height (cm)	Weight (kg)	Parity
Control	9	31 ± 2	163 ± 8	81 ± 13	3 ± 1
RL	8	31 ± 3	163 ± 10	73 ± 7	3 ± 1
NS	9	30 ± 4	160 ± 5	77 ± 11	2 ± 1

NS, normal saline; RL, Ringer's lactate.

Results

The three study groups were similar in age, height, weight, and parity (Table 1). Volumes of bupivacaine solution (0.75%) required to produce epidural anesthesia, time to induction, and degree of motor and sensory blockade at time of incision did not differ among groups (Table 2). The groups also had comparable durations of operation and similar degrees of sensory and motor blockade at the conclusion of surgery (Table 2).

Two dermatome sensory regression time (starting from the T-4 level at the conclusion of operation) did not differ among groups (control = 58 ± 29 min, $RL = 54 \pm 17 \text{ min}$, $NS = 47 \pm 20 \text{ min}$). However, groups receiving epidural crystalloid injections (both RL and NS) had significantly shorter durations of motor blockade (time from conclusion of operation to resolution of motor blockade) than did the control group (P < 0.005) (Figure 1). Times for resolution of motor blockade were more than twice as long in the control group than in either crystalloid group (control $= 178 \pm 70 \text{ min vs RL} = 84 \pm 44 \text{ min, NS} = 70 \pm 38$ min; P = 0.001) (Figure 1). When motor blockade had completely resolved, sensory level to pinprick was significantly higher in crystalloid groups (T-7) than in the control group (T-10) (P < 0.05). Thus, relative to motor blockade, sensory blockade resolved more slowly in the crystalloid groups than in controls $(control = 6.0 \pm 1.0, RL = 2.6 \pm 0.7, NS = 3.2 \pm 0.7)$ dermatomes). In fact, crystalloid administration did not significantly reduce duration of epidural analgesia, as reflected by similar times from termination of operation until first request for parenteral analysesics $(control = 216 \pm 132 min, RL = 161 \pm 108 min, NS =$ $175 \pm 66 \text{ min}$).

Plasma bupivacaine concentrations at the conclusion of operation did not differ among the three groups (control = 0.55 ± 0.20 mg/mL, RL = 0.58 ± 0.25 mg/mL, NS = 0.66 ± 0.34 mg/mL) (Table 3). At termination of the study (i.e., 45 min later), plasma bupivacaine concentrations had decreased in all groups (control = 0.38 ± 0.13 mg/mL, RL = 0.44 ± 0.22 mg/mL, NS = 0.52 ± 0.28 mg/mL) (Table 3). Mean decreases of plasma bupivacaine concentrations were similar in all groups.

Table 2.	Characterization of	Epidural	Blockade	Before	Experimental	Intervention
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Group	Volume of bupivacaine ^a (mL)	Anesthesia induction time (min)	Sensory level at incision	Motor blockade at incision (%)	Duration of surgery (min)	Sensory level at end of operation	Motor blockade at end of operation (%)
Control	24 ± 3	46 ± 18	T-4 ± 2	70 ± 25	57 ± 10	T-4 ± 2	70 ± 20
RL	26 ± 6	44 ± 17	T-4 ± 2	59 ± 15	57 ± 14	T-4 ± 2	54 ± 25
NS	25 ± 8	51 ± 16	T-4 ± 2	70 ± 20	65 ± 11	T-4 ± 2	55 ± 17

NS, normal saline; RL, Ringer's lactate.

^{*0.75%} bupivacaine; to establish surgical anesthesia.

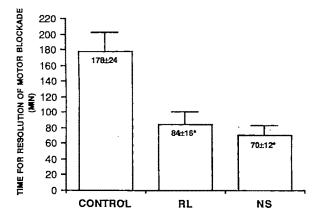


Figure 1. Effect of epidural crystalloid (RL = Ringer's lactate; $\overline{\text{NS}} = \text{normal saline}$) versus control on the time between conclusion of operation and complete resolution of motor blockade. Bar heights represent mean times, and error bars show sem. *P < 0.05.

In the epidural crystalloid groups, five patients experienced mild pressure dorsally during crystalloid injection, and several noted cool or wet sensations. No patient developed headache, nausea, vomiting, or persisting back pain. There were no immediate changes in vital signs, and there was no evidence of subsequent infection or neurologic sequelae.

Discussion

Persistence of motor blockade after epidural anesthesia can be a source of dissatisfaction to both patients and recovery-room staff. The present study demonstrates that crystalloid solutions (RL or NS), injected into the epidural space at the termination of operation, shorten the duration of bupivacaine-induced motor blockade without compromising sensory analgesia. Thus, the present findings suggest an approach to the problem of prolonged motor blockade.

The mechanism by which epidural injections of crystalloid solutions alter neural blockade is unclear. Intensity of epidural blockade may lessen because crystalloid solutions dilute local anesthetics in or adjacent to the epidural space, decreasing the con-

Table 3. Plasma Bupivacaine Concentrations Before and 45 min After Injection of Epidural Crystalloid^a

Group	п	A. Bupivacaine (µg/mL) before injection	B. Bupivacaine (μg/mL) after injection	Δ Bupivacaine ^b (μg/mL)
Control	6	0.55 ± 0.20	0.38 ± 0.13	0.16 ± 0.10
RL	7	0.58 ± 0.25	0.44 ± 0.22	0.13 ± 0.06
NS	7	0.66 ± 0.34	0.52 ± 0.28	0.14 ± 0.17

NS, normal saline; RL, Ringer's lactate.

"Values are mean ± sem.

centration of unbound drug at neuronal sites of action. Dilute solutions of bupivacaine would be expected to more effectively block sensory than motor nerves, thereby resulting in preferential sensory blockade as observed in our study (Table 2).

Alternatively, decreases in intensity could occur if crystalloid solutions enhanced clearance of local anesthetic from neural and connective tissues, or from the subarachnoid and epidural spaces. Saline injection into the epidural space appears to augment both secretion and clearance of CSF (6), and may therefore enhance elimination of local anesthetic from the subarachnoid space. Large volumes of fluid injected into the epidural space may also promote caudad and cephalad spread of drug, increasing surface area for uptake into blood vessels and lymphatics. Clearance of local anesthetics occurs via diffusion and uptake into lymph and blood vessels and is influenced by physicochemical properties (molecular weight, pKa, lipid solubility, and protein binding) of local anesthetics and their effects on spinal and epidural blood flow. However, enhanced clearance of local anesthetic from the epidural space does not appear to explain the preferential sensory blockade observed in our study because plasma bupivacaine concentrations did not differ among treatment groups (Table 3).

Theoretically, lowering the pH of solutions in the epidural space would enhance removal of anesthetics

^bReduction in bupivacaine concentration during 45-min study period, i.e., columns A – B.

from neural tissues by "trapping" the charged form of the molecule. With the slightly acidic crystalloid solutions (RL, pH 6.5, and NS, pH 5.0) used in the present study, nearly all of the bupivacaine (pKa, 8.1) in the epidural space would exist in the charged form (98% with RL, 99% with NS), as calculated by the Henderson-Hasselbach equation. (Limitations of the calculation include an unknown buffering capacity of the epidural space.) Perhaps, because of ion trapping of local anesthetic in the epidural space, the crystalloid injections did not affect blood bupivacaine concentrations (Table 3). Thus, the injections may not have altered the quantity of bupivacaine in the epidural space. Rather, the volume of fluid injected under pressure may have both diluted the local anesthetic and pushed the solution more cephalad, thereby preserving sensory blockade (i.e., reducing rate of regression) while decreasing intensity of motor blockade.

A potential problem with rapid fluid injection into the epidural space is that such injections can abruptly increase CSF pressure (7). In our study, 15-mL volumes of RL or NS were given over 1 min; in 28% of patients this was associated with transient, mild dorsal pressure; however, none complained of pain, stiff neck, or headache. This is similar to the experience with epidural blood patches, which involves injection of 15-20 mL of blood (less diffusible than RL or NS owing to greater viscosity) over 1–2 min without complications related to pressurization of the epidural space. Less rapid changes in CSF pressure would be expected with epidural infusions as compared with bolus injection of crystalloid. But would continuous infusions effectively shorten the duration of epidural anesthesia? A large bolus of crystalloid would probably act more rapidly than a comparable volume of solution infused over a long period of time.

The results of our study raise interesting questions. For example, could motor blockade be significantly shortened by a single injection of epidural crystalloid rather than the three injections given in the present study? Would subsequent withdrawal of injected fluid via the catheter enhance removal of local anesthetic from the epidural space? What effects would crystalloid injections have on duration of anesthesia produced by 0.75% bupivacaine in nonpregnant patients? (Although no longer indicated in obstetrics because of lower threshold for cardiotoxicity [8], 0.75% bupivacaine is commonly used in other patient populations.) Would effects differ for 0.5% bupivacaine? Would effects differ for highly lipophilic (e.g., bupivacaine, etidocaine) versus less lipophilic local anesthetics? Does epinephrine in the local anesthetic solution make a difference? Do crystalloid injections modify effects of previously administered epidural opioids? Birnbach et al. (9) reported that as diluent volume (NS) of a 50- μ g dose of epidural fentanyl is increased from 5 to 20 mL, onset time for analgesia is shorter and duration of analgesia increased. Thus, a large diluent volume may not only improve the pharmacokinetic profile of opioids, but could conceivably hasten recovery from local anesthetic-induced motor blockade, both intraoperatively and postoperatively.

A potential weakness of the present study is that it was merely single-blinded. We intended to doubleblind the study, but patients could not be truly blinded to treatment versus control group because they often had tactile sensation from solutions injected through the epidural catheter (despite sensory levels in the T-4 range). The likelihood of a placebo effect, however, was minimized by not informing patients of group assignment, by shamming injections (catheter manipulation) in the control group, and by avoiding inquiry about and discussion of sensations produced by epidural injections. Patient comments were recorded by anesthetists giving injections but were not communicated to investigators until the end of the study. Furthermore, investigators measuring motor and sensory blockade were not present during injections and were blinded to group assignments.

In conclusion, postoperative injections of a crystalloid solution (RL or NS) via epidural catheter markedly shortened the duration of motor blockade resulting from epidural anesthesia with bupivacaine (0.75%) used for cesarean delivery. Although these injections attenuated motor blockade, they did not significantly shorten duration of sensory anesthesia or postoperative analgesia. Whether this would occur in other patient populations or with other local anesthetics requires further study.

The authors thank Dr. Leroy Vandam for advice and editorial assistance and Pamela Vehring for technical, secretarial, and editorial assistance

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Effects of Epinephrine and Ritodrine in Dogs With Acute Hyperkalemia

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FOLLETT DV, LOEB RG, HASKINS SC, PATZ JD. Effects of epinephrine and ritodrine in dogs with acute hyperkalemia. Anesth Analg 1990;70:400-6.

As plasma potassium concentrations, whether normal or elevated, can be reduced by intravenous administration of either epinephrine or ritodrine, the effects of these drugs were examined during acute hyperkalemia. Six anesthetized dogs were studied every 2 wk, on 18 separate occasions. Hyperkalemia was induced by intravenous infusion of potassium chloride, resulting in plasma potassium concentrations of 9.6 ± 0.3 mEq/L (mean \pm sem), bradycardia, and idioventricular rhythm. Dogs were then given slow intravenous injections every 30 min of either saline (controls), epinephrine, or ritodrine. Epinephrine doses were 0.01, 0.1, 1.0, 10, 0, or $1000 \mu g/kg$; ritodrine doses were 0.1, 1.0, 10, 100, or $1000 \mu g/kg$. At the highest doses, both epinephrine and ritodrine caused clinically important de-

creases in plasma potassium, reduzing concentrations to below 7.0 mEq/L. Ritodrine had a significantly greater effect than epinephrine. Side effects included hypertension and dysrhythmias with epinephrine, serious hypotension with ritodrine, and tachycardia with both drugs. For both drugs, the doses that caused a decrease in plasma potassium also caused an increase in heart rate and there was a correlation between plasma potassium levels and heart rate. Epinephrine and ritodrine may be useful in treating acute hyperkalema, but cardiovascular side effects may occur. Increased heart rate could be used as an indicator of therapeutic effect and the magnitude of the increase in heart rate may be helpful in predicting the level of response.

Key Words: IONS, POTASSIUM—hyperkalemia. PHARMACOLOGY, RITODRINE—hyperkalemia treatment.

Numerous reports on adrenergic control of potassium homeostasis indicate that epinephrine decreases blood potassium levels in normokalemic and hyperkalemic humans and animals (1–5). This is due to potassium uptake by skeletal muscle and liver, and is mediated by β_2 -adrenergic receptors (2). Furthermore, hypokalemia has been reported after the use of the β -agonists ritodrine hydrochloride and terbutaline (6–8). Clinically, treatment of chronic hyperkalemia by administration of β_2 -agonists has been described (9–11). The purpose of this study was to compare the effects of epinephrine and ritodrine hydrochloride in a canine model of acute hyperkalemia. Our intent was to determine whether or not β_2 -agonists could be used in the treatment of acute hyperkalemia.

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Materials and Methods

The study was approved by the Animal Use and Care Committee of the University of California, Davis.

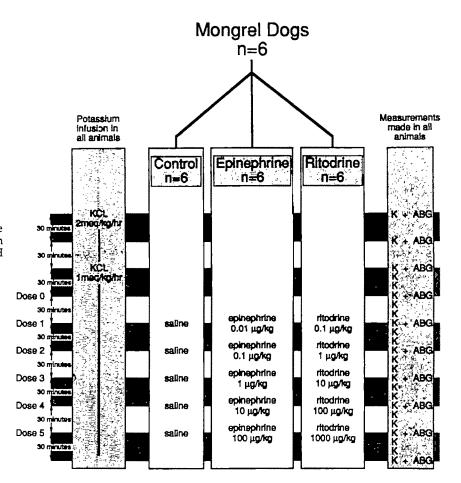
Six adult mongrel dogs were used for the study. Dogs were randomly allocated to each of three treatment groups using a 6×3 Latin square design. All dogs were given a minimum of 2 wk of rest between individual studies.

Dcgs were sedated with subcutaneous meperidine, 4 mg/kg, 30 min before each study. Anesthesia was induced with intravenous (IV) thiamylal, 10–20 mg/kg, the trachea was intubated, and anesthesia was maintained with 0.5%–2.0% isoflurane in oxygen.

A cephalic and a jugular vein were catheterized to provide IV access; a dorsal metatarsal artery was catheterized for blood pressure recording and arterial blood sampling. The electrocardiogram (ECG) and arterial blood pressure were recorded continuously with a Gould ES 1000 recorder (Gould, Inc., Cleveland, Ohio). Arterial pH and blood gas tensions were measured every 30 min with an Instrumentation

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<u>Figure 1</u>. Diagram of methods used in the three treatment groups. K = plasma potassium determination. ABG = measurement of pH and arterial blood gas tensions.

Laboratory 1340 pH and blood gas analyzer (Instrumentation Laboratories, Lexington, Mass.). Ventilation was controlled with a Bird Mark 7 ventilator (Bird Corporation, Palm Springs, Calif.); arterial carbon dioxide tension was maintained between 38 and 43 mm Hg. Sodium bicarbonate was infused intravenously, as required, to maintain base balance between −2 and +2 mEq/L. Isotonic saline was administered by continuous IV infusion at 2.5 mL·kg⁻¹·h⁻¹. Rectal temperature was maintained between 35 and 37°C.

Acute hyperkalemia was induced by administering potassium chloride (KCl) via the jugular catheter at 2 mEq·kg⁻¹·h⁻¹ for 1 h. Maintenance consisted of continuous infusion of KCl at 1 mEq·kg⁻¹·h⁻¹ for the remainder of the study. Plasma potassium levels were measured twice, at 30-min intervals, during the hour of KCl loading and every 10 min thereafter, with an Instrumentation Laboratory 443 flame photometer. After 1 h of administration of KCl at the maintenance rate, treatment was begun.

Treatment groups consisted of control studies, epinephrine studies, and ritodrine studies. The protocol followed for each study type is illustrated in Figure 1. In each study, five doses of test drug were administered by slow IV injection, one injection every 30 min.

Rate of IV injection ranged from 2 to 10 min depending on the animal's hemodynamic stability during the injection. In control studies, doses of test drug, numbered 1 through 5, were all 9 mL of isotonic saline. In epinephrine studies, doses 1 through 5 were (respectively) 0.01, 0.1, 1.0, 10, and 100 μ g/kg of epinephrine, each diluted in 9 mL of isotonic saline. In ritodrine studies, doses 1 through 5 were (respectively) 0.1, 1.0, 10, 100, and 1000 μ g/kg of ritodrine hydrochloride, each diluted in 9 mL of isotonic saline. Doses 1 through 5 of test drug were given sequentially to one dog during each study. At the end of each study, the KCl infusion was discontinued, and the dogs were allowed to recover from anesthesia.

The statistical significance of differences between treatment groups was determined by repeated measures analysis of variance and analysis of variance. If analysis of variance indicated a difference, unpaired Student's *t*-tests were used to determine significant differences between drugs at a particular dose for each effect. Plasma potassium concentration versus heart rate (HR) was analyzed by least-squares linear regression. Significant differences between linear regression slopes were determined by using unpaired





Figure 2. Lead II electrocardiogram recorded from a dog before KCl infusion (A), and after IV infusion of KCl at the maintenance rate (1 mEq·kg⁻¹·h⁻¹) for 4 h (B). In (A), the plasma potassium concentration was 3.8 mEq/L with an HR of 75 beats/min. In (B), the plasma potassium concentration was 9.5 mEq/L with an HR of 35 beats/min. The idioventricular rhythm noted in (B) is typical of this model.

Student's *t*-test. In all cases, differences were considered to be statistically significant if P < 0.05.

Results

Before treatment, after potassium loading, there were no significant differences in plasma potassium levels, mean arterial pressure (MAP), or HR between the three treatment groups. Plasma potassium concentration was 9.6 \pm 0.3 mEq/L (mean \pm sem). All dogs developed idioventricular ECG rhythms (Figure 2). Mean arterial pressure was 75 \pm 10 mm Hg; HR was 63 \pm 7 beats/min. Measured variables did not change significantly during the treatment portion of the control studies.

Both epinephrine and ritodrine caused doserelated decreases in plasma potassium concentrations after administration of dose 3 through dose 5 (Figure 3). At dose 5, ritodrine caused a statistically significant greater decrease in plasma potassium concentration than did epinephrine: 5.2 ± 0.6 versus 6.0 ± 0.7 mEq/L.

Both epinephrine and ritodrine converted the idioventricular rhythm to a sinus rhythm once the plasma potassium concentration decreased below 7.0 mEq/L. Paroxysmal premature ventricular contractions were seen with epinephrine after dose 4 and dose 5. These two doses were administered very slowly (up to 10-min injection time in some dogs) to prevent malignant arrhythmias during injection.

Both epinephrine and ritodrine changed MAP (Figure 4). After administration of dose 5, epinephrine increased MAP to 125 ± 20 mm Hg. After administration of dose 4 and dose 5, ritodrine decreased MAP to 60 ± 5 and 45 ± 5 mm Hg, respectively. These two doses were administered very slowly (up to 10-min injection time in some dogs) to prevent severe hypotension during injection. At dose 5, there was a statistically significant difference between the blood pressure effects of the two drugs.

Both epinephrine and ritodrine caused an increase in HR at doses 3 through 5 (Figure 5). At doses 4 and 5, these increases were significantly greater with ritodrine (150 \pm 10 versus 70 \pm 10 beats/min and 205 \pm 10 versus 115 \pm 10 beats/min, respectively).

The drug-induced changes in plasma potassium, MAP, and HR always occurred within 10 min of injection of test drug. There was no consistent pattern of change in these parameters at 20 and 30 min after injection, regardless of dose. As a result, the data presented in the dose-response figures (Figures 3–5) are derived from the average of the parameters measured at 10, 20, and 30 min after each dose.

Plasma potassium levels and HR responses were similar to each other for both of the test drugs. Plasma potassium levels began to decrease and HR began to increase at a common threshold dose, dose 3 (Figures 3 and 5). Additionally, there was a significant correlation between plasma potassium concentration and HR during treatment with epinephrine and ritodrine, but not during potassium loading before administration of test drugs (Figure 6). The relationship between plasma potassium concentration and HR for each test drug was such that for any given plasma potassium concentration, the corresponding HR tended to be greater with ritodrine than with epinephrine, but this difference was not statistically significant (Figure 6).

Discussion

Common protocols for treatment of acute hyperkalemia include IV administration of either insulin and dextrose or sodium bicarbonate to promote cellular uptake of plasma potassium, and IV administration

Figure 3. Plasma potassium concentration (mean ± sem) as a function of dose number (see Figure 1) for epinephrine and ritodrine in six dogs during KCl infusion (1 mEq·kg $^{-1}$ ·h $^{-1}$). The time-course between each dose is 30 min. Each plasma potassium value represents the average of three samples collected at 10-min intervals during the 30-min period between doses. Both drugs decreased plasma potassium concentration. At dose 5 (100 μg/kg epinephrine or 1000 μg/ kg ritodrine), there was a statistically significant greater decrease in plasma potassium concentration with ritodrine, compared to that with epinephrine. *P < 0.05 difference between groups.

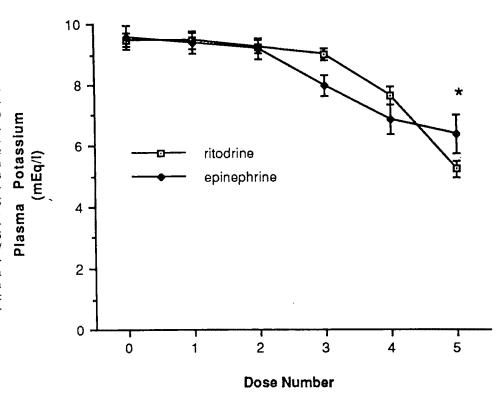
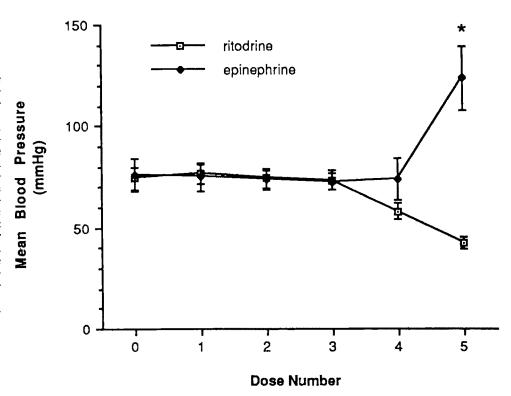


Figure 4. Mean blood pressure (mean ± sem) as a function of dose number (see Figure 1) for epinephrine and ritodrine in six dogs during KCl infusion (1 mEq·kg $^{-1}$ ·h $^{-1}$). The time-course between each dose is 30 min. Each blood pressure value represents the average of three blood pressures recorded at 10-min intervals during the 30min period between doses. Both drugs altered blood pressure. Epinephrine caused hypertension; ritodrine caused hypotension. At dose 5 (100 μ g/kg epinephrine or 1000 μ g/kg ritodrine), there was a statistically significant difference between the hypertensive response to epinephrine and the hypotensive response to ritodrine. $^*P < 0.05$ difference between groups.



of calcium (gluconate or chloride) to reduce membrane threshold potential and restore normal membrane excitability (12,13). Insulin and dextrose therapy decreases plasma potassium levels within 30 min (12,13). Potential problems with this therapy include

hyperglycemia (14), volume overload (14), and hypoglycemia (12). Sodium bicarbonate reportedly causes a rapid decrease in plasma potassium, but can cause tetany in patients in whom serum calcium levels are low (13). In a recent study (12), however, IV

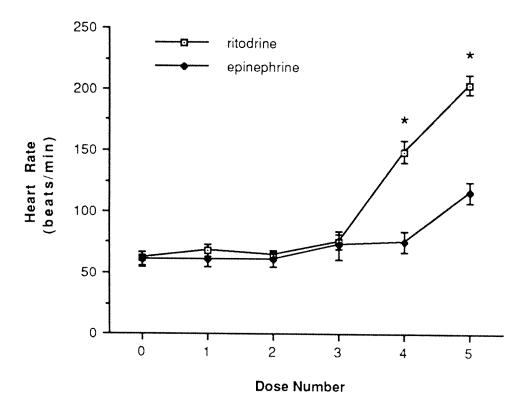


Figure 5. Heart rate (mean ± SEM) as a function of dose number (Figure 1) for epinephrine and ritodrine in six dogs during KCl infusion $(1 \text{ mEq} \cdot kg^{-1} \cdot h^{-1})$. The timecourse between each dose is 30 min. Each HR value represents the average of three HRs recorded at 10-min intervals during the 30-min period between doses. Both drugs increased HR. At dose 4 (10 μ g/ \tilde{k} g epinephrine or 100 µg/kg ritodrine) and dose 5 (100 µg/kg epinephrine or 1000 μ g/kg ritodrine), there was a statistically significant greater increase in HR with ritodrine, compared to that with epinephrine. *P < 0.05 difference between groups.

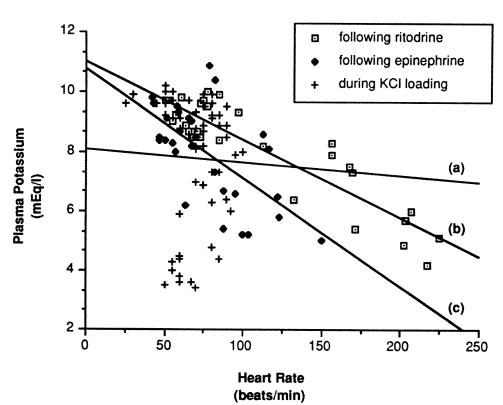


Figure 6. Correlation between plasma potassium concentration and HR during KCl infusion based on individual data points in six dogs (total) in each of three groups; during potassium loading (a), after ritodrine (b), and after epinephrine (c). There is a linear correlation between plasma potassium and HR during treatment with epinephrine (r = 0.399, n = 30), and ritodrine (r = 0.809, n = 30), but not during potassium loading before treatment (r = 0.001, n = 59).

 bicarbonate failed to lower plasma potassium levels in patients with terminal renal failure, but did increase plasma bicarbonate levels and pH. Calcium therapy rapidly stabilizes hyperkalemia-induced ECG

changes, but it does not lower the extracellular potassium concentration, and its effects are very transient (13). It has been suggested that β_2 -agonists represent a viable alternative to these other therapies

for hyperkalemia (14). Our study was performed to determine the dose range and therapeutic ratio of two β_2 -agonists when used for the management of acute hyperkalemia in dogs. Epinephrine was chosen because it is commonly used in the management of patients with cardiac arrest; and hyperkalemia often precipitates cardiac arrest. Ritodrine was chosen because it is one of the few β_2 -agonists commercially available for parenteral use. We chose the doses of the test drugs based on pilot data and clinical experience; doses were not chosen based on equal potency.

Unlike the present study, previous hyperkalemia models did not control acid-base balance or measure hemodynamics, and have been criticized for being "unphysiologic" (15). Our model mimics an acute hyperkalemic crisis, is stable and reproducible, and lends itself readily to future studies of hyperkalemia. Although we administered β_2 -agonists by IV injection, treatment by infusion could also be studied using this model.

Our study has the limitation of using a sequence of increasing drug doses, and as a result, there might be some cumulative drug effect. A series of randomized doses, with time allowed between doses for a return to baseline, although perhaps more ideal, was not possible for budgetary reasons. We believe that these cumulative drug effects are minimal as each subsequent dose represents a 10-fold increase over the previous dose.

On the basis of the present study, it appears that either epinephrine or ritodrine may be used to treat acute hyperkalemia. Both drugs significantly reduced plasma potassium concentrations and converted a potassium-induced cardiac arrhythmia to sinus rhythm. As these effects arise from potassium redistribution rather than a decrease in total body potassium, treatment of the underlying cause of hyperkalemia is still required. Epinephrine administered by continuous IV infusion in patients suffering from terminal renal failure tended to decrease plasma potassium in only 5 of 10 patients studied (12). These trends were slight (5.6 \pm 0.3 to 5.3 \pm 0.3 mmol/L), and were not statistically significant. The difference between the results and conclusions of that study and those of our study could be due to the method of epinephrine administration (continuous IV infusion versus IV bolus), the total dose of epinephrine used, the duration of the hyperkalemia (chronic versus acute), the greater intracellular stores that exist in renal failure patients, or the fact that our pretreatment plasma potassium concentrations were greater $(9.6 \pm 0.3 \text{ mEg/L versus } 5.4-5.7 \text{ mmol/L}).$

Treatment of hyperkalemia with epinephrine and

ritodrine should be undertaken with caution, especially in patients with cardiovascular disease. Both drugs may produce undesirable side effects such as hypotension, hypertension, tachycardia, and premature ventricular contractions. Some of these effects were minimized in our study by administering the drugs over longer periods of time (up to 10 min) or by momentarily stopping administration of the drugs. We assume that these problems can also be minimized by administering the drugs as a continuous IV infusion rather than as an IV bolus.

The relationship between changes in plasma potassium concentration and changes in HR with the test drugs is not a direct cause-and-effect relationship. The lack of correlation between these parameters during potassium loading indicates that the relationship is one of covariance with a third factor. It is likely that this third factor is β_2 -receptor activity.

We administered both test drugs over a wide dose range to bracket the dosages for each drug that would be maximally therapeutic with the least undesirable side effects. At this time, we cannot directly predict doses for clinical practice, whether veterinary or human. However, based on this study, we are able to generalize about drug dosage. Undesirable effects with these drugs are dose-dependent, and it is likely that acceptable (but not maximal) decreases in plasma potassium concentration can be attained with minimal adverse effects. In this study, the optimal dose for epinephrine was at least 1.0 μg/kg, but less than 100 μ g/kg; the dose for ritodrine was at least 10 μ g/kg, but less than 1000 μ g/kg. Further data are needed to determine an optimal dose range for each drug in humans. In any event, β_2 -agonist therapy for acute hyperkalemia should be monitored with an ECG and blood pressure and plasma potassium measurements. Increases in HR will likely herald decreases in plasma potassium.

The authors gratefully acknowledge the technical assistance of Dr. Goro Ishizaki (deceased), and dedicate this article to his memory.

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Dexmedetomidine Premedication for Minor Gynecologic Surgery

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AANTAA RE, KANTO JH, SCHEININ M, KALLIO AMI, SCHEININ H. Dexmedetomidine premedication for minor gynecologic surgery. Anesth Analg 1990;70:407-13.

The effects of four different doses (0.167, 0.33, 0.67, and 1.0 μ g/kg) of dexmedetomidine, a novel α_2 -adrenoceptor agonist, on anesthetic requirements, hemodynamics, and plasma catecholamine levels were investigated in a singleblind fashion in 20 healthy (ASA physical status I) women scheduled for uterine dilatation and curettage. The drug was administered intravenously 15 min before anesthesia induction with thiopental. Nitrous oxide/oxygen (70%/30%) was used for maintenance. Dexmedetomidine was well tolerated, and no serious drug-related subjective side effects or adverse events were observed. The most prominent

subjective effects were tiredness and decreased salivation. The total amount of thiopental needed to perform uterine dilatation and curettage was decreased dose-dependently from 400 ± 166 mg (mean \pm 5D) after 0.167 µg/kg of dexmedetomidine to 180 ± 65 mg after 1.0 µg/kg of dexmedetomidine (P = 0.028). Blood pressure, heart rate, and plasma norepinephrine levels were reduced after dexmedetomidine. The optimal dose of dexmedetomidine for single-dose intravenous premedication studies in minor surgery appears to be in the range of 0.33-0.67 µg/kg.

Key Words: PREMEDICATION, DEXMEDITOMIDINE. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—dexmedetomidine.

Benzodiazepines, opiates, barbiturates, and histamine- and β -adrenoceptor antagonists, as well as anticholinergic agents, have traditionally been used as preoperative medication to eliminate or to suppress the stress reaction to anesthesia and surgery and to control the fear and anxiety experienced by many patients. It has recently become evident that α_2 -adrenoceptor agonists may also be a useful class of drugs in conjunction with anesthesia (1,2). They simultaneously potentiate the effects of general anesthetic agents, reduce their dose requirements, and attenuate sympathoadrenal responses to noxious stimuli encountered during anesthesia and surgery, thus providing improved hemodynamic, metabolic, and hormonal stability (3).

Clonidine, an α_2 -agonist widely employed in the therapy of hypertensive illness, has, for example, recently been reported to have beneficial effects (i.e.,

sedation, analgesia, anxiolysis, improved perioperative hemodynamic stability) when used as preoperative treatment or as an additional medication during anesthesia (4–13).

Medetomidine, a specific α_2 -agonist (14), has a considerably higher α_2/α_1 -selectivity ratio than clonidine in receptor binding experiments (1620 vs 220) (14), and, compared with the latter drug, it is more effective as an α_2 -agonist in most pharmacologic models tested so far (14–16). Medetomidine exerts a sympatholytic effect presumably by activating inhibitory α_2 -adrenergic receptors both in the central nervous system and on peripheral sympathetic nerve endings (presynaptic autoreceptors) (16,17). These actions lead to inhibition of the release of norepinephrine from sympathetic nerve endings (18,19). The inhibition of sympathetic transmitter release can be measured in humans as a decrease in the concentration of norepinephrine in plasma (20).

Medetomidine is a 1:1 racemic mixture of optical isomers of which the *d*-isomer, dexmedetomidine (MPV-1440), is pharmacologically active (21). Dexmedetomidine has effectively reduced anesthetic requirements in animals as measured by MAC (21–24) and may even be a complete anesthetic by itself in sufficiently high doses in certain animal models (24).

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Table 1. Patient and Operation Characteristics

Dose	Age (yr)	Weight (kg)	Duration of operation (min)
0.167 μz/kg	40.2 ± 2.8	67.6 ± 15.4	9.0 ± 2.6
0.33 μg/kg	43.2 ± 3.7	66.8 ± 9.6	10.4 ± 4.3
0.67 μg/kg	43.2 ± 4.6	70.2 ± 13.8	15.5 ± 8.1
1.0 μg/Eg	44.8 ± 4.4	57.2 ± 6.3	9.4 ± 7.3
All subjects	42.8 ± 4.0	65.45 ± 12.0	10.84 ± 5.9
One-way ANOVA			
F	1.19	1.15	1.13
P	0.34	0.36	0.37

ANCVA, analysis of variance. Valu≘s are mean ± sp.

The aims of this study were to assess the sedative, hemodynamic, and anesthetic-reducing effects of dexmedetomidine, as well as the optimal dose of intravenous dexmedetomidine as premedication before uterine dilatation and curettage (UD&C) under thiopental/nitrous oxide anesthesia. This is the first report of clinical experience with dexmedetomidine as premedication before anesthesia in humans.

Patients and Methods

Patients

Twenty healthy (ASA physical status I) nonpregnant women who were scheduled for UD&C were included in this study (age, 42.8 ± 4.0 yr [mean ± sp]; weight, 65.4 ± 12.0 kg) (Table 1). They were admitted to the hospital only for gynecologic reasons, and none received any medication other than that used in connection with anesthesia. The study protocol was approved by the Ethics Committee of Turku University Hospital and the Finnish National Board of Health. Written informed consent was obtained from each patient.

Methods

Four coses of dexmedetomidine were used (0.167, 0.33, 0.67, and 1.0 μ g/kg), with five subjects at each dose level. The subjects were divided randomly into four groups. This dose-finding study was conducted in a single-blind fashion.

The patients entered the hospital a day before the scheduled surgery. After fasting overnight, and after at least 1 h of rest in the supine position, the patients were transferred to the operating unit at least 30 min before UD&C. Our studies took place between 9 AM

and 12 noon and were performed in a quiet room with a constant dim light. Uterine dilatation and curettage itself was performed in a standard operating theater. After the arrival of the patient in the operating unit, continuous monitoring of the electrocardiogram and noninvasive recordings of systolic (BPS) and diastolic (BPD) blood pressure and heart rate (HR) with an automated oscillometric device (Nippon Colin 203Y, Tokyo, Japan) were started. An antecubital vein on the left arm was cannulated to administer the premedication and the anesthetic (thiopental), as well as to collect blood samples. The cannula was kept patent with a dilute heparin solution. Blood samples were collected before premedication and at induction of anesthesia, at the end of the operation, and 30 and 60 min after recovery for determination of the concentrations of the catecholamines norepinephrine and epinephrine, the deaminated catecholamine metabolite 3,4-dihydroxyphenylglycol (DHPG), and cortisol.

Dexmedetomidine was administered slowly (over 60 s) intravenously 15 min before anesthesia and UD&C. Anesthesia was induced with thiopental in small increments of 25–50 mg at 15-s intervals, and the induction dose (enough to suppress the eyelid reflex) was recorded (25). Anesthesia was maintained with nitrous oxide/oxygen (70%/30%; fresh gas flow, 9 L/min), and a modified Mapleson F (Jackson Reese) system was used for ventilation. If spontaneous movements occurred, small additional doses (25 mg) of thiopental were given to produce sufficient anesthesia. The time needed to regain consciousness after termination of nitrous oxide (i.e., when the patient opened her eyes at verbal command) was recorded.

After UD&C and recovery from anesthesia, the patients were observed and tested for 1 h. Impairment of vigilance was objectively assessed with the Maddox Wing and the critical flicker fusion test (26,27). Visual analogue scales (patient marking on a 100-mm-long horizontal line; VAS) were used to obtain subjective estimates (28,29) on the experience of fear, anxiety, mental clouding, tiredness, dryness of mouth, nausea, headache, and pain. The subjects were urged to report any possibly drug-related subjective symptoms, and a standardized side-effect questionnaire was repeated as indicated in Figure 1.

Blood for the chemical determinations was collected into chilled polypropylene tubes with potassiumethylenediaminetetraacetate; these tubes were stored in ice until centrifuged within 2 h at 0°–4°C. The plasma samples were stored at -70°C until assayed.

Levels of endogenous catecholamines in venous plasma were determined using high-performance liquid chromatography with coulometric electrochemi-

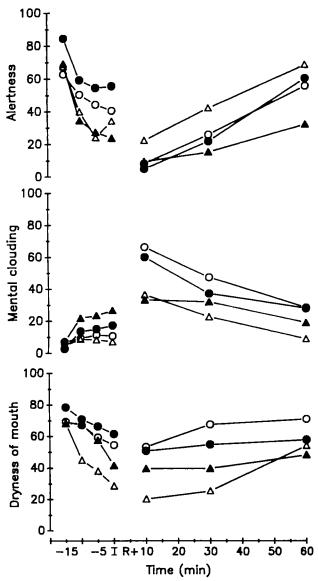


Figure 1. Mean values for subjectively measured alertness, mental clouding, and dryness of the mouth (as millimeters on a 100-mmlong visual analogue scale: 0 = asleep, no confusion, or very dry mouth; 100 = fully alert, very confused, normal salivation). Symbols: 0.167 (O), 0.33 (\blacksquare), 0.67 (\triangle), and 1.0 (\blacktriangle) $\mu g/kg$ dexmedetomidine (I = induction of anesthesia; R = recovery from anesthesia). Time point -15 min is before premedication.

cal detection, which allows measurement of both catecholamines and the deaminated metabolite DHPG in a single run (30). The reproducibility of the assay was tested using pooled plasma samples from previous clinical studies, and the resulting intraassay coefficients of variation were less than 2% for norepinephrine, approximately 4% for DHPG, and approximately 10% for epinephrine in the relevant concentration ranges. All the samples from one experimental session were analyzed in one assay.

The concentrations of cortisol in plasma were analyzed using commercially available radioimmunoassay kits (Cortisol [125I] Radioimmunoassay Kit, Farmos Diagnostica, Turku, Finland) with intraassay coefficients of variation below 5% in the relevant concentration range.

Statistics

Statistical analysis was performed using one-way analysis of variance (ANOVA) or analysis of variance for repeated measurements with one between-factor (dose) and one within-factor (time). When a statistically significant dose effect or dose-time interaction was found, the analysis was continued using contrasts for each pair of dose levels. Some variables were tested for linear and quadratic trends as a function of drug dose.

The statistical analysis of the VAS and vigilance data was performed over two periods of time: from the start of the experiment until the time of induction and from recovery until the end of the procedure.

The statistical analysis of changes in BPS, BPD, and HR was performed over two periods of time: from the start of the study until the end of UD&C and from the recovery until the end of the procedure.

The statistical analysis of plasma levels of catecholamines and cortisol was performed over the time period from 15 min before induction until the end of the procedure.

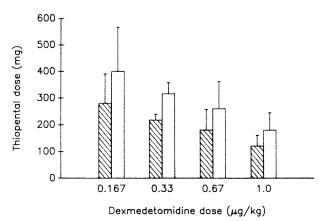
Results

The different dose groups were roughly equal in weight, age, and duration of operation (Table 1). Dexmedetomidine was well tolerated, and no serious hemodynamic or other possible drug-related adverse events were observed.

Fearfulness, anxiety, and alertness decreased and mental clouding increased after dexmedetomidine administration, as measured by VAS (F = 4.46 and P = 0.0077, F = 8.74 and P = 0.0001, F = 24.46 and P < 0.0001, and F = 9.23 and P = 0.0001, respectively) (Figure 1). These changes were not statistically significantly dose-dependent, although the two largest doses (0.67 and 1.0 μ g/kg) tended to have the greatest effects.

The objective evaluation of vigilance with the Maddox wing before induction did not reveal statistically significant differences between the doses.

Dexmedetomidine induced a clear and statistically significant increase (F = 20.75 and P < 0.0001) in



<u>Figure 2</u>. The mean dose (±sp) of thiopental after different doses of dexmedetomidine premedication (*shaded bars* indicate the induction dose and *open bars* the total dose).

mouth dryness (Figure 1). This effect lasted until the end of the study, and there was a statistically almost significant dose-time interaction (F = 2.35 and P = 0.054) in ANOVA.

The amount of thiopental needed for UD&C was significantly dependent on the dexmedetomidine dose (F = 3.93 and P = 0.028, one-way ANOVA). The total amount of thiopental used for UD&C was 400 \pm 166 mg after the lowest dose (0.167 μ g/kg) and 180 \pm 65 mg after the highest dose (1.0 μ g/kg) (Figure 2). When tested for trends, a statistically significant decreasing linear trend (F = 11.72 and P = 0.0035) was found. The induction dose of thiopental, as well as the total dose, also showed a dose-dependent reduction (F = 4.49 and P = 0.018, one-way ANOVA). The induction dose after the lowest dose $(0.167 \mu g/kg)$ was 280 ± 110 mg; after the highest dose (1.0 μ g/kg), it was 120 \pm 41 mg (Figure 2). A significant decreasing linear trend (F = 13.3 and P =0.0022) was found. The maintenance dose was 120 \pm 135 mg after the lowest dose and 60 ± 45 mg after the highest dose (F = 0.56 and P = 0.65, one-way ANOVA).

There was a decrease of BPS (F = 4.42 and P = 0.0002) after all doses of dexmedetomidine (Figure 3) before induction. This decrease was not dose-dependent (F = 0.44 and P = 0.73). The maximal effect was seen 10 min after drug administration. During UD&C, BPS varied a lot; but after the highest dose (1.0 μ g/kg), BPS was consistently at its lowest level. After recovery, there was a dose-dependent decrease (F = 2.82 and P = 0.042) as well as a decrease as a function of time (F = 5.45 and P < 0.0001) in BPS. Again, after the highest dose BPS was consistently lowest (Figure 3).

Diastolic blood pressure also decreased after all doses of dexmedetomidine (F = 5.01 and P < 0.0001). This effect, maximal 5–10 min after administration of

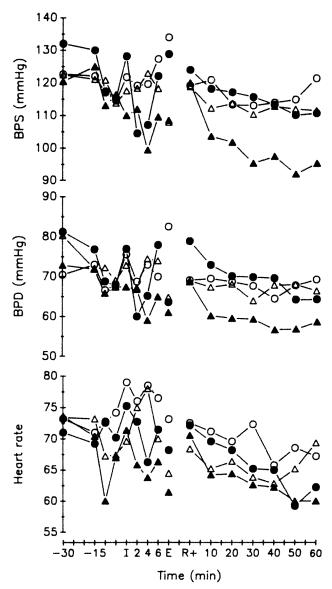
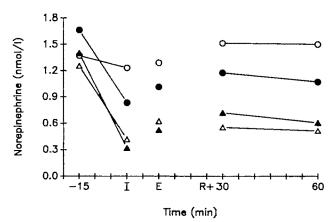


Figure 3. Mean values of BPS and BPD and HR. Symbols as in Figure 1. (I = induction of anesthesia; E = end of the operation; and R = recovery from anesthesia. Note the different time scale during anesthesia.)

the drug (Figure 3), was not dose-dependent (F = 0.28 and P = 0.84). After recovery, BPD was consistently lowest after the highest dose ($1.0~\mu g/kg$), but the differences between the doses were not statistically significant (F = 1.81 and P = 0.15).

Analysis of variance revealed an almost significant dose-time interaction in HR recordings (F = 1.60 and P = 0.061) during the time from the start of the study until the end of UD&C. Heart rate was decreased after the two highest doses (0.67 and 1.0 μ g/kg) of dexmedetomidine (from initial mean values of 73.2 \pm 9.5 and 70.4 \pm 4.2 to 67.2 \pm 11.8 and 60.0 \pm 9.3 beats/min, respectively, at 10 min after injecting the drug). In contrast to the two higher doses, HR



<u>Figure 4.</u> Mean plasma norepinephrine concentrations. Symbols as in Figure 1.

<u>Table 2</u>. Two-Way Analysis of Variance for Repeated Measurements (ANOVA) on the Plasma Concentrations of Catecholamines and Cortisol

Variable	Factor 1 (dose)	Factor 2 (time)	Interaction
Norepinephrine			
F	3.00	11.02	1.31
P	0.062	< 0.0001	0.24
Epinephrine			
F	1.09	0.50	0.82
P	0.38	0.74	0.63
DHPG			
F	1.23	7.38	2.19
P	0.33	0.3001	0.023
Cortisol			
F	1.34	5.59	0.35
P	0.30	0.3006	0.98

DHPG, 3,4-dihydroxyphenylglycol.

increased slightly after the smaller doses (0.167 and 0.33 μ g/kg). During UD&C, HR varied markedly in all groups, but after the smallest dose (0.167 μ g/kg) HR was consistently highest (Figure 3). Heart rate had a declining trend after recovery. This trend was statistically significant as a function of time (F = 7.69 and P = 0.0001), but no differences could be demonstrated between the drug doses (F = 0.41 and P = 0.75).

The smallest dose (0.167 μ g/kg) of dexmedetomidine did not change the norepinephrine concentration in plasma, but the two highest doses (0.67 and 1.0 μ g/kg) decreased the plasma norepinephrine levels to one-third of the initial values 15 min after drug administration (Figure 4). In overall ANOVA, the dose effect was almost significant (P = 0.062; see Table 2). In a pairwise comparison of the dose groups, the norepinephrine concentrations after the two highest doses differed significantly from those after the smallest dose (F = 6.39 and P = 0.022 for

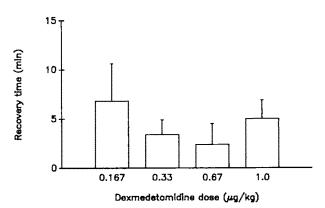


Figure 5. Effect of different doses of dexmedetomidine premedication on the mean (±sp) recovery time from thiopental nitrous oxide + oxygen anesthesia.

0.167 vs $0.67 \mu g/kg$ and F = 5.56 and P = 0.031 for 0.167 vs $1.0 \mu g/kg$). Anesthesia and UD&C were not associated with significant increases in the plasma norepinephrine concentrations in any of the groups.

There was a significant dose-time interaction (F = 2.19 and P = 0.023) in ANOVA of the DHPG concentrations in plasma, with a monotonously decreasing tendency over the entire observation time after the two highest dexmedetomidine doses (Table 2). In the pairwise comparisons, the smallest dose (0.167 μ g/kg) differed significantly from all other doses.

There were no consistent changes in the plasma epinephrine concentrations after the administration of dexmedetomidine (Table 2).

The cortisol concentrations did not change after drug administration or during UD&C, but 30 min after recovery an increase was observed in all dose groups. The increases were not significantly different between the drug doses (Table 2).

The time needed to regain consciousness after termination of nitrous oxide administration was dose-dependently decreased by dexmedetomidine (from 6.8 ± 3.8 min after $0.167~\mu g/kg$ of dexmedetomidine to 2.4 ± 2.1 min after $0.67~\mu g/kg$). After the highest dose ($1.0~\mu g/kg$), the duration of recovery was again longer (5.0 ± 1.9 min) than after the two intermediate doses (0.33 and $0.67~\mu g/kg$) (Figure 5). This difference in recovery times after the various dexmedetomidine doses did not quite reach statistical significance in one-way ANOVA (F = 2.99 and P = 0.062), but when tested for trends, a significant quadratic trend (F = 7.26 and P = 0.016) was found.

The patients in the two highest dose groups (0.67 and 1.0 μ g/kg) recovered from anesthesia fastest as measured by VAS on the basis of changes in alertness and mental clouding. The difference between the doses did not reach statistical significance, although some trends may be seen in Figure 1. The Maddox wing and critical flicker fusion tests did not reveal

significant differences between the groups in the speed of recovery.

There were no statistically significant differences in the incidence of headache, pain, or nausea. In fact, the scores on these VAS variables remained low throughout the study. Only one patient (in the 0.33- μ g/kg dose group) required analgesic supplementation (Oxycodone 5 mg intravenously and 5 mg intramuscularly) for lower abdominal pain after UD&C.

Discussion

Surgical procedures, endotracheal intubation, and anesthesia are stressful to the patient and may induce potentially harmful reactions—such as increases in the secretion of catecholamines and other stress hormones, and increases in HR and blood pressure (31–33). Patients with a history of hypertension or coronary artery disease are particularly prone to hyperdynamic cardiovascular responses to stressful events encountered during surgery (34). There is a clear relationship between surgical events known to produce intense sympathetic stimulation and perioperative myocardial ischemic episodes and postoperative myocardial infarction (35). Effective attenuation of the sympathoadrenal stress responses is thus an important goal in modern anesthesiology, especially in high-risk patients.

Single intravenous doses of dexmedetomidine $(0.167-1.0~\mu g/kg)$ were well tolerated by the 20 healthy female patients in this study having minor gynecologic operations under thiopental/nitrous oxide anesthesia. Apart from sedation and decreased salivation, no subjective symptoms or possible drugrelated adverse events were detected.

In the present study, dexmedetomidine induced marked and sustained reductions in the plasma concentrations of norepinephrine, implicating decreased sympathetic nervous activity (Figure 4). This reduction of sympathetic transmitter release was accompanied by small decreases in blood pressure and HR (Figure 3).

Dexmedetomidine decreases the required amount of volatile anesthetics, and is even a complete anesthetic in itself in certain animal models (21,22,24). The mechanism of this action is not clear, but it has been suggested that dexmedetomidine and other α_2 -agonists reduce anesthetic requirements by acting on both presynaptic and postsynaptic α_2 -adrenoceptors in the central nervous system. Recent animal studies have in fact suggested predominant involvement of postsynaptic α_2 -adrenoceptors in the effects of dexmedetomidine on the molecular mechanisms mediating the anesthetic response (21,24).

The total amount of thiopental needed for anesthesia was substantially decreased (from 400 ± 166 mg after $0.167~\mu g/kg$ to 180 ± 65 mg after $1.0~\mu g/kg$) by the higher doses of dexmedetomidine premedication in the present study. The decrease in the total amount of thiopental was mostly due to a reduction in the induction dose. The slower recovery after the highest $(1.0~\mu g/kg)$ dose of dexmedetomidine than after the intermediate doses $(0.33~and~0.67~\mu g/kg)$ may indicate that this dose is higher than optimal. It may produce undesirably long and strong effects in combination with thiopental, although the amount of thiopental used was smallest after this, the largest dose.

There was a clear decrease in the experience of fear and anxiety after dexmedetomidine administration. After recovery from anesthesia, mental clouding and tiredness decreased fastest after the 0.67- μ g/kg dose of dexmedetomidine. This is most likely attributable to the lesser amount of thiopental needed for the completion of the operation after this dose.

After the 0.67-µg/kg dose, recovery was fastest as measured by the time required to regain consciousness. The decrease in the duration of recovery after this dose compared to the other doses may in part be due to the slightly longer duration of UD&C itself in this dose group, although this difference did not reach statistical significance (Table 1).

Decreased salivation is a known side effect of clonidine as an antihypertensive in clinical practice (36), but it may also be a desirable effect in many types of anesthesia and surgery. In the present study, the increased experience of dryness of the mouth lasted until the end of the procedure (Figure 1). Dryness of the mouth and sedation, as well as the hemodynamic actions of dexmedetomidine, closely resemble the effects induced by clonidine, but dexmedetomidine has a shorter duration of action (37). This agrees with a mean elimination half-life of 2.3 h for dexmedetomidine in healthy male volunteers (data on file, Farmos Group Ltd.), compared with 7.7 h for clonidine (36).

In conclusion, single doses of intravenously administered dexmedetomidine caused a dose-dependent decrease in the amount of thiopental needed to perform UD&C. As a result of this reduced amount of thiopental, dexmedetomidine decreased the recovery time after the operation. There were moderate reductions in BPS and BPD as well as in HR, together with substantial decreases in the plasma concentrations of norepinephrine after the administration of dexmedetomidine. The most favorable results were obtained after the 0.67- μ g/kg dose of dexmedetomidine, as the time required to regain consciousness was

shortest and the recovery of alertness fastest. An optimal dose of dexmedetomidine for single-dose intravenous premedication studies in minor surgery appears to be in the range of $0.33-0.67 \mu g/kg$.

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Treatment of Postoperative Paralytic Ileus by Intravenous Lidocaine Infusion

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RIMBĂCK G, CASSUTO J, TOLLESSON P-O. Treatment of postoperative paralytic ileus by intravenous lidocaine infusion. Anesth Analg 1990;70:414–9.

The effects of continuous intravenous infusion of lidocaine on postoperative paralytic ileus in cholecystectomized patients was investigated in this double-blind study. An infusion of lidocaine (3 mg/min, n=15) or an infusion of an equal volume of saline (n=15) was started 30 min before induction of anesthesia and continued for 24 h after surgery. Postoperative colonic motility was evaluated by radicpaque markers and serial abdominal radiographs. A record was kept of the first passage of gas and feces. Results showed significantly earlier return of propulsive motility in the colon of lidocaine-treated patients. Radiopaque markers in the lidocaine group were propelled significantly earlier from the cecum/ascending colon to the transverse colon (P < 0.05) and appeared significantly earlier in the descending colon (P < 0.05) and the rectosigmoid colon

(P < 0.05) than in saline-treated patients. Despite the fact that the mean time for postoperative defecation occurred 17 h earlier in lidocaine-treated patients, differences between the groups were not statistically significant—a fact due, perhaps, to great individual variations in defecation habits. The time to first passage of gas, a variable representative of changes in anorectal or colonic tone rather than propagative motility, also did not differ significantly between the groups. No adverse reactions to lidocaine were reported. The results suggest that continuous intravenous infusion of lidocaine during the first postoperative day shortens the duration of paralytic ileus in the colon after abdominal surgery. Supression of inhibitory gastrointestinal reflexes by reduction of postoperative peritoneal irritation is suggested as the mechanism of action.

Key Words: ANESTHETICS, LOCAL—lidocaine. GASTROINTESTINAL TRACT, PERISTALSIS—postoperative.

The inhibition of gastrointestinal motility after major abdominal surgery can sometimes be extensive and of considerable clinical significance. Postoperative adynamic ileus is characterized by nausea, inability to take oral feedings, and abdominal distention (1). This inhibition is most pronounced in the stomach (2) and colon (3). The mechanisms responsible for the development of adynamic ileus are not fully clarified, although several studies suggest that nociceptive stimulation of the peritoneum inhibits gastrointestinal motility by activation of inhibitory reflexes (1,4).

Several studies have shown an excitatory effect of local anesthetics on intestinal smooth muscle both in vitro (5–10) and after topical and systemic adminis-

tration in vivo (11,12), suggesting that these agents act by blocking inhibitory reflexes within the intestinal wall and thereby releasing spontaneous myogenic activity (9). A previous study demonstrated that intraperitoneal administration of a local anesthetic could shorten the period of postoperative colonic inhibition in patients undergoing abdominal surgery (13). The aim of the present study was to evaluate the effect of continuous intravenous (IV) infusion of lidocaine on postoperative colonic inhibition in cholecystectomized patients measured radiologically using radiopaque markers.

Materials and Methods

All subjects fasted for at least 12 h before the operation. Preanesthetic medication consisted of 0.05–0.075 mg fentanyl and 2.50–3.75 mg droperidol intramuscularly. Anesthesia was induced with thiopental (5 mg/kg). After the administration of 1 mg pancuronium to prevent fasciculations, tracheal intubation was done with the use of succinylcholine (1 mg/kg).

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After intubation, 5 mg pancuronium was given with additional doses of 1 mg as indicated during surgery. Anesthesia was maintained with nitrous oxide and oxygen, and with a bolus injection of 0.1-0.2 mg of fentanyl at the induction of anesthesia followed by $0.003 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. At the conclusion of surgery, 1 mg atropine followed by 2.5 mg neostigmine were administered to reverse neuromuscular blockade. Postoperative pain relief was achieved by intramuscular injections of meperidine. Intravenous infusions were restricted to isotonic saline or Ringer's lactate solutions during the first postoperative day. A questionnaire concerning postoperative nausea, vomiting, and possible adverse reactions to lidocaine was filled out by the patients on the morning of the first postoperative day. In all patients arterial blood pressure, heart rate, and oscilloscopic electrocardiogram were monitored throughout the duration of infusion of lidocaine or saline placebo.

Thirty patients scheduled for elective cholecystectomy were studied. All patients gave written informed consent and the protocol was approved by the Regional Ethics Committee and the Radiation Safety Committee. Preoperative bowel habits were investigated and patients with stool frequency between three stools daily and three stools weekly were included. Patients using laxatives or drugs known to affect gastrointestinal motility and patients with a history of gastrointestinal disease or complications to surgery were excluded. All women capable of child-bearing were asked about their menstrual cycle. When the possibility of pregnancy could not be minimized, the patient was not included.

Patients were randomly allocated to receive double-blind IV bolus injections of 100 mg lidocaine (n = 15) 30 min before anesthesia followed by a continuous IV infusion of lidocaine at 3 mg/min (2 g lidocaine in 500 mL isotonic saline). The infusion was continued for 24 h after completion of surgery. Injection and infusion of similar volumes of isotonic saline were administered in the placebo group (n = 15).

Measurement of Colonic Propulsive Motility

Four types of radiopaque markers were prepared: 10×2 -mm cylindrical tubes (type 1), 17×2 -mm cylindrical tubes (type 2), 10×2 -mm cylindrical tubes filled with barium sulfate powder and sealed at the ends (type 3), and 17×2 -mm barium-filled cylindrical tubes (type 4). All markers were cut from a radiopaque tube with a specific gravity of 1.4 (Tubing 2501, Meadox Surgimed, Denmark). Four markers, one of each type, were enclosed within two gelatin

capsules. Patients swallowed the markers at 8 PM on the evening before surgery. The shape and size of each marker was such that they were easily distinguished from each other on the radiographs.

Location of radiopaque markers within the intestinal tract on abdominal films was determined by gaseous outlines of the colon. In cases where colonic outlines were unclear, bony landmarks as described by Arhan et al. (14) were used for localization. Transit of the markers was followed by plain abdominal radiographs. The first radiograph was taken immediately after the operation, and another was taken at 8 AM on the second postoperative day, with radiographs every 12 h thereafter until the markers had reached the rectosigmoid colon or until a maximum of eight radiographs were taken. The radiographs were analyzed by a radiologist who was unaware of the group to which the patients belonged. The colon was outlined on the radiographs and divided into four segments: segment 0 (cecum and ascending colon), segment 1 (transverse colon), segment 2 (descending colon), and segment 3 (rectosigmoid colon). Starting from the end of surgery, the time taken for the fastest marker to reach each segment of the colon postoperatively was recorded. The choice of the fastest marker as indicator for propulsive motility was based on the propagative properties of the markers evaluated by comparison with water-soluble iodine contrast (15,16). In cases where markers were propelled across the border of more than one segment on two consecutive radiographs, the time for the passage through intermediary segment(s) was considered to be equal to the time for the markers to reach the distal segment.

Total colonic transit ranging from the end of surgery until markers had reached the rectosigmoid colon is equal to the time for the markers to reach segment 3 (Figure 1). Calculations of colonic transit time after the reappearance of postoperative propulsive motility were based on the time range between the last observation of the radiopaque markers in the ascending colon (segment 0) and the time they reached the rectosigmoid colon (segment 3). Patients in whom the markers had not reached segment 3 before the last radiograph were excluded from calculations of colonic transit time.

Starting on the morning of the first postoperative day, all patients were offered a standardized meal consisting of liquid and solid foods three times per day. The patients recorded on a questionnaire the date and hour for the first postoperative passage of gas and feces and the time (hours) was calculated from the termination of surgery.

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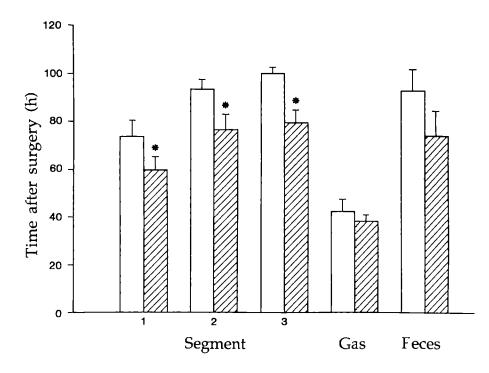


Figure 1. Time taken for the radiopaque markers in the cecum/ascending colon (segment 0) to reach other segments of the colon and the time for the first postoperative passage of gas and feces in patients receiving IV infusion of lidocaine (shaded bars) or isotonic saline infusion (open bars). Segment 1 (transverse colon); segment 2 (descending colon); segment 3 (rectosigmoid colon). *P < 0.05 vs control. Data are expressed as mean ± SEM.

Statistical Methods

Comparisons of segmental colonic motility were made using the log rank test for censored observations (17) taking into consideration patients in whom markers had not reached segment 2 or segment 3 before the last radiograph. All other intergroup differences were analyzed by the Wilcoxon rank sum test. Data are mean \pm SEM.

Results

The two groups of patients were similar with regard to age, weight, sex distribution, and the duration of surgery (Table 1). The dose of fentanyl given during surgery did not differ significantly between the groups (Table 1). The need for meperidine was significantly lower in the lidocaine group during the first (P < 0.05) and second postoperative days (P < 0.05) (Table 1). The incidence of postoperative nausea and vomiting was similar in both groups (P > 0.05) (Table 1). Systolic blood pressure and pulse rate during the first postoperative day did not differ significantly in the two groups of patients (P > 0.05), and no electrocardiogram abnormalities were reported. No subjective side effects due to possible lidocaine overdose were reported except for sedation in two patients.

Colonic Propulsive Motility

In all but five patients, all four markers we found in the cecum or ascending colon on the radiograph

<u>Table 1</u>. Demographic Data in 30 Patients Undergoing Cholecystectomy Under General Anesthesia With 24-h Intravenous Infusion of Lidocaine or Saline

	Saline	Lidocaine
Number	15	15
Age (yr)	51 ± 3	55 ± 3
Sex (F/M)	9/6	10/5
Weight (kg)	73 ± 4	70 ± 3
Duration of surgery (min)	104 ± 8	109 ± 7
Nausea	9	6
Vomiting	7	8
Fentanyl during surgery (mg)	0.42 ± 0.03	0.45 ± 0.03
Meperidine (mg)		
1st postoperative day	143 ± 24	92 ± 19*
2nd postoperative day	69 ± 15	12 ± 4^{a}
3rd postoperative day	15 ± 8	10 ± 3

Values are mean ± sem.

taken immediately after surgery. In these five patients (two lidocaine and three controls), one of the markers was located in the ileum but was transported into the cecum before any propagative colonic motility could be registered. The start of propulsive motility in the colon after surgery, as indicated by the propagation of radiopaque markers from the cecum (segment 0) to the transverse colon (segment 1), occurred significantly earlier in lidocaine-treated patients than in control patients (P < 0.05) (Figure 1). Markers reached both the descending colon (segment 2) and the rectosigmoid colon (segment 3) significantly more rapidly in the lidocaine group than in the control group (P < 0.05) (Figure 1). In four patients,

 $^{^{\}bullet}P < 0.05$ vs control group.

two from each group, the markers did not reach the rectum before the last radiograph. These patients were not included in the calculations of colonic transit time. Transit through the colon after the reappearance of propulsive colonic motility (colonic transit time) was 27 ± 5 h in the lidocaine group and 32 ± 5 h in the control group (P > 0.05).

There were no statistically significant differences between the two groups regarding the time for the first postoperative passage of gas or feces (P > 0.05) (Figure 1).

Discussion

This study shows that IV lidocaine infusion significantly shortens the duration of postoperative colonic paralysis after major abdominal surgery as measured by the propagation of radiopaque markers. The mechanisms by which lidocaine could influence colonic motility can be several. A direct excitatory effect on intestinal smooth muscle has been demonstrated by several authors in animal experiments after administration of local anesthetics both in vitro (5–10) and after topical and systemic administration in vivo (11,12). Such a direct effect is not likely to explain our results, as propulsive motility returned 36 h after ending the lidocaine infusion.

Systemic administration of opiate analgesics both stimulates and inhibits propulsive colonic motility (18). It could be assumed that the effects of IV lidocaine on colonic motility are indirect by reducing pain and, subsequently, the need for opiate analgesics in the postoperative period. Such a mechanism cannot be ruled out, although Wilson (19) found that postoperative opiates do not influence the duration of paralytic ileus in patients after undergoing abdominal surgery. Moreover, a previous study investigating the effects of epidural anesthesia on postoperative adynamic ileus after cholecystectomy failed to demonstrate prolonged inhibition of postoperative colonic motility in control patients receiving significantly larger amounts of pentazocine after surgery than patients receiving epidural blockade (20).

The stimulatory actions of lidocaine on postoperative colonic motility could also be due to blockade of the afferent and/or efferent link of the sympathetic inhibitory spinal and prevertebral reflexes suggested to be involved in the pathophysiology of adynamic ileus (1,4). Several studies have demonstrated a significant depression of spike activity, response amplitude, and conduction time in myelinated A-delta and unmyelinated C-fibers following systemic administration of local anesthetics (21–24). These data favor

the idea that systemic local anesthetics influence the duration of paralytic ileus by suppression of activity in primary afferent neurons from the abdominal cavity involved in reflex inhibition of gut motility (1,4). Intravenous infusion of lidocaine has also been shown recently to reduce urine output of catecholamines 48 h after surgery (25). This long-lasting inhibition of the sympathoadrenal response to surgery may add to the beneficial effects of lidocaine on paralytic ileus, as circulating catecholamines have been shown to play a role in postoperative gastrointestinal inhibition (26).

In view of the fact that even relatively brief intraabdominal surgery may paralyze the gut for a period of several days (27), postoperative ileus must involve an intraabdominal process that maintains the inhibitory intestinal reflexes well beyond the duration of surgery. Abdominal surgery, for example, is associated with damage to the peritoneal surface (28) that elicits an inflammatory response with release of inflammatory agents such as histamine, serotonin, bradykinin, and prostaglandins (29). These agents have potent direct activating effects on afferent nerve fibers (30,31) and indirect effects by sensitization of receptors to noxious stimuli (32). The inflammatory reaction in the area of surgery could be responsible for the activation and maintenance of abdominal reflexes responsible for the long-lasting inhibition of colonic motility after surgery.

Local anesthetics of the amide group have potent antiinflammatory properties. MacGregor et al. (33) have shown that the IV infusion of lidocaine significantly inhibits the development of experimental aseptic peritonitis in rabbits. Similarly, intraperitoneal administration of local anesthetics has been shown to induce potent inhibition of peritonitis (34) and to reduce the duration of postoperative adynamic ileus in cholecystectomized patients (13). The antiinflammatory effects of lidocaine involve inhibition of prostaglandin synthesis (35), inhibition of the migration of granulocytes into the inflammatory area (33,36), and inhibition of granulocyte release of lysosomal enzymes (37) and their production of tissue-toxic oxygen-free radicals (38). Recent data suggest that these antiinflammatory effects of local anesthetics are long-lasting (39,40). Thus, by inducing a prolonged inhibition of peritoneal irritation after major abdominal surgery, lidocaine may interfere with the activation and maintenance of inhibitory intestinal reflexes responsible for the development of paralytic ileus.

The lack of difference between the groups regarding the first passage of gas can be explained by previous data showing no significant correlation between the first postoperative passage of gas and

propulsive motility in the colon as shown by radiopaque markers and water-soluble iodine contrast (15,16), suggesting that the first passage of gas only represents increased tonic activity in the colon or anorectum after surgery rather than the onset of propulsion. Despite the fact that the mean time for the first postoperative passage of feces occurred 17 h earlier in the lidocaine group, the difference between the groups was not statistically significant. These results can be explained by data showing that the first passage of feces is a variable subject to great variations due to individual defecation habits (15,16). Another possible explanation could be the distinct functional differences between the anorectum, which is responsible for the maintenance and expulsion of colonic contents partly under the control of conscious will, and the rest of the colon, which is primarily involved in propulsion strictly under autonomous control (41).

In conclusion, we have shown that continuous IV infusion of lidocaine during the first postoperative day after cholecystectomy can reduce the need for narcotics and shorten the period of postoperative colonic inhibition in patients undergoing major abdominal surgery. The stimulatory effects of lidocaine on the paralytic gut probably involve several mechanisms, although we suggest that the long-term effect of lidocaine on paralytic ileus is secondary to the inhibition by lidocaine of peritoneal irritation followed by reduced activation of inhibitory gastrointestinal reflexes.

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Lower Esophageal Sphincter Integrity Is Maintained During Succinylcholine-Induced Fasciculations in Dogs With "Full" Stomachs

William P. Cook, MD, and Raymond R. Schultetus, MD, PhD

COOK WP, SCHULTETUS RR. Lower esophageal sphincter integrity is maintained during succinylcholine-induced fasciculations in dogs with "full" stomachs. Anesth Analg 1990;70:420–3.

During succinylcholine-induced muscle fasciculations, gastroesophageal barrier pressure in fasted adult dogs (n = 10) was compared by esophageal manometry with that in the same dogs with full stomachs. After fasting, fasciculations did not increase significantly either mean intragastric pressure (4.7 \pm 1.3 mm Hg before; 5.2 \pm 1.7 mm Hg during) or lower esophageal sphincter pressure (35.4 \pm 21.4 mm Hg before; 40.6 \pm 17.5 mm Hg during). Filling the dogs' stomachs with 300 mL of saline significantly

increased both mean intragastric pressure (from 3.8 ± 2.2 to 7.4 ± 1.4 mm Hg) and mean lower esophageal sphincter pressure (from 20.2 ± 6.8 to 28.6 ± 14.8 mm Hg). Fasciculations did not produce a further increase in either mean intragastric or mean lower esophageal sphincter pressure. Most importantly, in all animals, under all conditions, gastroesophageal barrier pressure remained positive (range, 6.0–65.5 mm Hg) and therefore served as a barrier to passive regurgitation.

Key Words: GASTROINTESTINAL TRACT, ESOPHAGUS, STOMACH. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE.

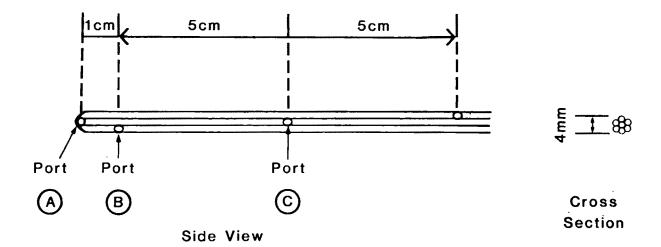
Succinylcholine increases intragastric pressure. The magnitude of this increase is directly related to the intensity of muscle fasciculations (1,2). Investigators have reasoned that this increase in intragastric pressure may cause regurgitation of gastric contents into the oropharynx and thus lead to pulmonary aspiration. They have therefore recommended attenuating the fasciculations with a prior dose of nondepolarizing muscle relaxant (1,2). However, this reasoning ignores the major barrier to gastroesophageal reflux, the intrinsic tone of the lower esophageal sphincter (LES) (3-6). Intragastric pressure must exceed LES pressure before reflux can occur. Thus, other investigators (5,7-12) coined the term "barrier pressure" (BrP), which is the difference between LES pressure and intragastric pressure. Recent studies have demonstrated that BrP is maintained in both humans and dogs during succinvlcholine-induced muscle fasciculations, despite an increase in intragastric pressure (13,14). However, these studies were performed in fasted human volunteers and dogs. Thus, we reasoned that in the case of a full stomach, in which resting intragastric pressure and volume are higher, BrP might be overcome by the onset of succinylcholine-induced muscle fasciculations.

Methods

After approval by the All-University Committee on the Care and Use of Laboratory Animals at our institution, 10 healthy, mongrel dogs were selected. All dogs were fasted for 10-12 h. Anesthesia was induced with thiopental (7 mg/kg) and was maintained with additional thiopental as needed. The dogs were mechanically ventilated with 100% oxygen via an endotracheal tube to maintain a Paco₂ of 36 ± 3 mm Hg. A multilumen, polyvinyl, esophageal manometry catheter was introduced through the esophagus into the stomach of each dog. One lumen opened at the distal tip of the catheter (Figure 1, A); the remaining lumens had ports on the side that were spaced at 5-cm intervals from the tip. The catheter was positioned so that the most distal side port (Figure 1, B) was in the stomach and the next proxi-

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<u>Table 1</u>. Intragastric and Lower Esophageal Sphincter (LES) Pressures in 10 Dogs at Baseline, With a Saline-Filled Stomach, and During Fasciculations

	Period 1	Period 2
After fasting		
Intragastric (mm Hg)	4.7 ± 1.3	3.8 ± 2.2
LES	35.4 ± 21.4	20.2 ± 6.8
Saline-filled stomach		
Intragastric (mm Hg)		$7.4 \pm 1.4^{\circ}$
LES		28.6 ± 14.8^{b}
During fasciculations		
Intragastric (mm Hg)	5.2 ± 1.7	11.1 ± 4.6
LES	40.6 ± 17.5	31.5 ± 16.1

Values are mean ± sp.

<u>Table 2</u>. Barrier Pressures in 10 Dogs After Fasting, With a Saline-Filled Stomach, and During Fasciculations

	Barrier pressure (mm Hg)			
	After fasting	Full stomach	Fasciculations	
Period 1				
Mean (sp)	31.1 ± 22.2	_	35.3 ± 18.6	
Range	8.3-65.0	_	10.0-58.0	
Period 2				
Mean (sp)	16.5 ± 7.0	21.3 ± 13.8	20.5 ± 16.4	
Range	5.9-26.1	8.0-57.4	6.0-65.6	

mal side port (Figure 1, C) was in the high-pressure zone of the LES. Normal saline (2 μ L/s) was infused through disposable continuous-flush valves (American Pharmaseal) in the two side ports.

Intragastric and LES pressures were recorded through these two side ports by using transducers (Bentley Trantec, model 800) and a polygraph (Grass Instruments). After these measurements, succinylcholine (2 mg/kg, intravenous) was administered, and intragastric and LES pressures were recorded

<u>Figure 1</u>. End and side views of the esophageal manometry catheter constructed with seven polyvinyl hollow catheters bonded together. To study LES integrity, port C was positioned in the high-pressure zone of the LES, and ports A and B were in the lumen in the stomach. Intragastric and LES pressures were measured via ports B and C, respectively.

again during fasciculations. After recovery from neuromuscular blockade and anesthesia, the trachea was extubated and the dog was returned to the kennel (period 1). The same measurements were repeated at 4–14-day intervals in the same dogs (period 2), except that before succinylcholine was administered, the dogs' stomachs were filled rapidly (3–4 min) with 300 mL of normal saline via the lumen that opened at the catheter tip. Succinylcholine (2 mg/kg, intravenous) was immediately administered, and the intragastric and LES pressures were recorded during fasciculations.

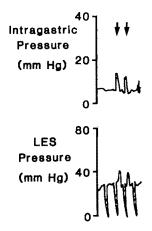
Pressures during the same time period were compared by the Wilcoxon signed rank test and between the time periods by analysis of variance.

Results

At baseline mean intragastric and LES pressures did not differ significantly between period 1 and period 2 (Table 1). After the dogs' stomachs were filled with saline in period 2, the mean intragastric pressure and mean LES pressure increased significantly (Table 1). Fasciculations from succinylcholine did not significantly increase any further the mean intragastric pressure or mean LES pressure in either period (Table 2). Although intragastric pressure increased in a few dogs during fasciculations, in all dogs during both gastric conditions BrP remained positive (range, 6.0–65.5 mm Hg) (Table 2).

 $^{^{\}circ}P < 0.01$ when compared with after-fasting values.

 $^{^{}b}P < 0.05$ when compared with after-fasting values.



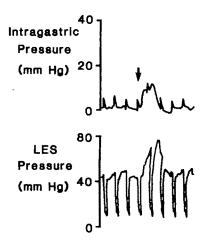
<u>Figure 2</u>. This recording of intragastric pressure (top) and LES pressure (bottom) demonstrates the simultaneous increase in LES and intragastric pressures observed in a dog when the abdomen was compressed manually to simulate increased intraabdominal pressure. Negative deflections occur in the recording of LES pressure when positive pressure ventilation momentarily displaces the side port of the catheter from the LES.

Discussion

Elevating intraabdominal and intragastric pressures by applying external pressure to the abdomen has resulted in a concomitant increase in LES pressure in human volunteers (15). Similar results in dogs (14) and in humans (16-18) have been described and were reproduced by us in pilot studies in dogs (Figure 2). Increasing intraabdominal pressure from peritoneal insufflation during laparoscopy also increases LES pressure (19). The mechanisms for this concomitant increase in intragastric and LES pressures is not understood; some data support a neural reflex arc (15,17,20); other data support a strictly mechanical effect (16,18,21). Apparently, this mechanism increases LES pressure when an increase in intragastric volume or fasciculation increases intragastric pressure (Figure 3).

In our study, LES and intragastric pressures in dogs after fasting agree in general with those reported in other studies of dogs (22) and humans (1,11,17,23,24). Lower esophageal sphincter pressure can vary significantly in an individual at various times (5); indeed, we noted that within the same animal LES pressure varied as much as 50 mm Hg when measured on different days after fasting. However, during the experimental periods in our study, LES pressure remained constant.

The manner in which LES pressure is recorded is important. A high-fidelity, noncompliant recording system and a continuous fluid infusion is necessary for accurate and reproducible results. Our system met criteria proposed for fidelity (25). The LES in dogs has about the same length, anatomic location, pressure characteristics, and physiologic response to



<u>Figure 3</u>. This recording of intragastric pressure (*top*) and LES pressure (*bottom*) demonstrates the simultaneous increase in LES and intragastric pressure that was typically observed in dogs after succinylcholine was administered (indicated by *arrow*).

swallowing as that in humans (22); therefore, the results of our study in dogs are likely applicable to humans. However, one must be cautious when extrapolating the results of animal studies to humans.

It is possible that the 300 mL of normal saline infused into the stomachs of the study dogs did not fill the stomach. The amount of saline we used, 300 mL, corresponds to approximately 18 mL/kg, or 1200 mL of fluid in a 70-kg human, which would certainly fill a human stomach. In addition, during pilot studies we performed necropsy to confirm that the dogs' stomachs were enlarged and filled. It is doubtful that any significant amount of saline from the stomach entered the duodenum, because the total time from initiation of saline infusion to measuring pressures during fasciculations was less than 5 min; during this time intragastric pressure was elevated and constant. To avoid undue manipulation of the LES, baseline gastric volume was not measured in this study. The period of fasting we used (10-12 h) has been confirmed, by numerous investigations in our laboratory, to produce as closely as possible an empty stomach.

During a rapid sequence induction, one of the reasons for injecting a small dose of a nondepolarizing muscle relaxant before administering succinylcholine is to attenuate fasciculations and to reduce or prevent an increase in intragastric pressure, which might lead to regurgitation. Because the small dose of nondepolarizing muscle relaxant does not prevent fasciculations reliably, may interfere with succinylcholine-induced paralysis, and occasionally may produce significant paralysis, this use of a nondepolarizing agent has been questioned (26,27). Our study did not determine whether an exceptionally high increase in intragastric pressure (reported occasion-

ally to be as high as 26 mm Hg [2]) can overcome LES pressure in dogs with full stomachs because the highest intragastric pressure in our study was 18 mm Hg. However, studies in humans have shown increases in LES pressure high enough to prevent gastroesophageal reflux when intraabdominal pressure reaches 25 mm Hg (16).

Incompetence of the LES may result from certain physiologic conditions (e.g., during pregnancy) (11,22,28), may be drug-induced (e.g., by atropine and other anticholinergics) (9,10,14,29), or may, in an otherwise healthy person, accompany symptoms of gastroesophageal reflux (3). In these special situations, the results of our study may not apply.

In summary, intragastric pressure increased substantially, as expected, when dogs' stomachs were filled with saline. However, LES pressure also increased simultaneously, which maintained BrP while stomachs were full and also during succinylcholine-induced fasciculations.

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Evaluation of a Forced-Air System for Warming Hypothermic Postoperative Patients

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LENNON RL, HOSKING MP, CONOVER MA, PERKINS WJ. Evaluation of a forced-air system for warming hypothermic postoperative patients. Anesth Analg 1990;70:424–7.

Thirty adult surgical patients admitted to the recovery room with an oral temperature ≤35.0°C were randomized into two groups. Group 1 patients were covered with cotton blankets warmed to 37.0°C, and group 2 patients were treated with a forced-air warming system. Mean oral temperature on admission to the recovery room was the same in both groups (34.3°C). Oral temperature and the presence or absence of shivering were recorded at 15-min intervals. After application of the selected warming method,

patients in group 2 were warmer at all time intervals. Mean temperatures in the forced-air heating group and in group 1 were, respectively, 34.8°C and 34.3°C (P < 0.05) at 15 min; 35.0°C and 34.2°C (P < 0.01) at 30 min; 35.2°C and 34.5°C (P < 0.05) at 45 min; 35.8°C and 34.7°C (P < 0.001) at 60 min; 36.0°C and 35.0°C (P < 0.01) at 75 min; and 36.0°C and 35.0°C (P < 0.01) at 90 min. The incidence of shivering was significantly greater in group 1 at 15 and 45 min. In addition, time spent in the recovery room was significantly greater in group 1 than in group 2, 156.0 min versus 99.7 min (P < 0.003).

Key Words: HYPOTHERMIA, POSTOPERATIVE. TEMPERATURE, BODY—postoperative.

Despite intraoperative efforts at prevention, hypothermia (temperature < 36.0°C) after anesthesia and surgery is present in 53%–85% of adult patients at the time of admission to the recovery room (1–3). Severe hypothermia may lead to ventricular fibrillation or to a standstill both of which are resistant to therapy (4). More commonly, hypothermia is not life-threatening. In response to hypothermia, however, adults increase heat production by shivering. The metabolic cost of shivering is high. Oxygen consumption may increase by 300%-800% (5-7). Arterial hypoxemia, metabolic acidosis, and cardiovascular instability may result if this increased oxygen consumption is not compensated for with increases in cardiac output and ventilation (5,7,8). Prolonged postoperative hypothermia is reported to be associated with increased mortality after surgery (2).

Attempts at rewarming hypothermic patients have included various types and combinations of warming

blankets (electric, water-filled, gel-filled), metalized plastic blankets, heating lamps, and warm cotton blankets. Few data on rewarming in the postanesthesia care unit are available, and no completely satisfactory method for warming hypothermic postoperative patients has been reported (9). In the present study, we compared the efficiency of a forced-air heating system (Bair Hugger, Augustine Medical, Inc.) with covering patients with warmed cotton blankets for postoperative rewarming.

Methods

This study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from all patients. Thirty adult surgical patients (aged 18–70 yr) who had been admitted to the recovery room with oral temperature ≤ 35.0°C were randomly assigned by sealed envelope to one of two groups. Group 1 patients were covered from neck to feet with cotton blankets warmed to 37.0°C; group 2 patients were treated with the Bair Hugger system. This system consists of a disposable patient cover and a heat source. The cover is made of plastic and paper bonded into tubular channels with slits through

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Table 1. Patient Characteristics

Group	Age (yr)	Height (cm)	Weight (kg)
1 (cotton blankets) $(n = 15)$	59.0 ± 15.0	164.5 ± 8.9	60.3 ± 9.3
2 (forced-air warming) (n = 15)	59.3 ± 14.9	161.1 ± 9.7	65.7 ± 11.7

Values are mean ± sp.

which warm air flows around the patient. The heat source consists of a 400-watt heating element with fan, a microprocessor-based temperature controller limited to a maximum of 43°C (110° F), a hose connecting the heat source output to the patient cover, and a 5- μ m filter within the connecting hose.

Patients who were febrile, hemodynamically unstable, or mechanically ventilated; those who were having blood products infused or required vasoactive drugs; and those with underlying muscle, central nervous system, or autonomic disorders were excluded. All study patients had been anesthetized with isoflurane, nitrous oxide in oxygen, and fentanyl. Oral temperature and the presence or absence of shivering were recorded upon admission to the recovery room and at 15-min intervals until discharge. Oral temperatures were measured with a Diatek digital thermometer (Diatek, Inc.) calibrated according to the manufacturer's guidelines.

The changes in oral temperature as a function of time in the two groups were analyzed using a regression analysis for grouped data. This avoids the discarding of information occurring when only the mean values of the dependent variable are used in the regression analysis (10). The slopes of the regression lines were compared using Student's *t*-test. The significance of differences in temperature between the two groups at each measurement was evaluated using Student's unpaired *t*-test. The significance in the incidence of shivering at each time interval in the two groups was determined utilizing a one-tailed Fisher's exact test. The duration of time spent in the

recovery room was compared between the two groups using Student's unpaired t-test. Differences were considered statistically significant when P < 0.05.

Results

There were no complications with either method for warming hypothermic postsurgical patients. Patients were comparable in regard to age, height, and weight (Table 1). Mean oral temperature on admission to the recovery room was the same in both groups, 34.3°C.

After application of the selected warming method, patients in the forced-air warming group were significantly warmer at all time intervals measured than were those in the cotton-blanket group (Table 2). Mean oral temperature in the forced-air warming group had risen to 34.8°C 15 min after entering the recovery room; patients in the cotton-blanket group remained at 34.3°C (P < 0.05). At succeeding intervals, temperatures in the forced-air heating group compared with the cotton-blanket group were, respectively, 35.0°C and 34.2°C (P < 0.01) at 30 min; 35.2°C and 34.5°C (P < 0.05) at 45 min; 35.8°C and 34.7° C (P < 0.001) at 60 min; 36.0° C and 35.0° C (P < 0.001) 0.01) at 75 min; and 36.0°C and 35.0°C (P < 0.01) at 90 min (Table 2). The incidence of shivering on arrival in the recovery room was not significantly different between groups, although patients in group 1 experienced significantly more shivering 15 and 45 min after entering the recovery room than patients in group 2 (Table 3). The incidence of shivering between groups 30 min after arrival in the recovery room approached but did not achieve statistical significance (P = 0.057). Patients in group 1 spent significantly more time in the recovery room than did patients in group 2: 156.0 min vs 99.7 min (P < 0.003).

The regression line describing the relationship between oral temperature and time in group 1 patients was defined by the formula y = 0.021x + 34.38, where x = time (min) and y = temperature (°C)

<u>Table 2</u>. Oral Temperatures in Patients Warmed With the Forced-Air Heating System or Cotton Blankets Measured at 15-min Intervals After Admission to the Recovery Room

				Time (min)			
Group	0	15	30	45	60	75	90
1 (cotton blankets)	34.3 ± 0.6 $(n = 15)$	34.3 ± 0.6 $(n = 15)$	34.2 ± 0.9 $(n = 15)$	34.5 ± 1.0 $(n = 15)$	34.7 ± 1.0 $(n = 15)$	35.0 ± 1.1 $(n = 15)$	35.0 ± 1.0 $(n = 15)$
2 (forced-air warming)	34.3 ± 0.5 (n = 15)	$34.8 \pm 0.7^{\circ}$ (n = 15)	35.0 ± 0.7^{b} (n = 15)	$35.2 \pm 1.0^{\circ}$ $(n = 15)$	35.8 ± 0.6^{c} $(n = 15)$	36.0 ± 0.6^{b} $(n = 13)$	36.0 ± 0.4^b $(n=9)$

Values are mean \pm sp. Number of patients is shown in parentheses.

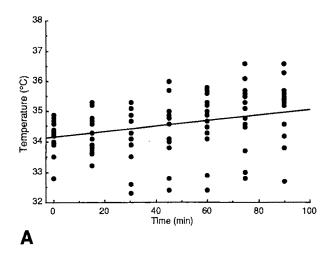
 $^{^{\}circ}P < 0.05$ vs cotton blankets.

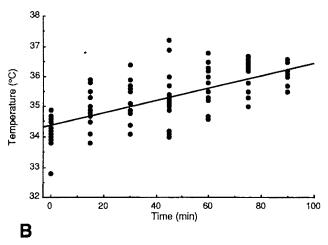
 $[^]bP < 0.01$ vs cotton blankets. $^cP < 0.001$ vs cotton blankets.

<u>Table 3</u>. Incidence of Postoperative Shivering in 15-Min Intervals in Patients Warmed With the Forced-Air Heating System Versus Cotton Blankets

Group				Time (min)			
	0	15	30	45	60	75	90
1 (cotton blankets)	11	10	9	8	4	0	0
2 (forced-air warming)	(n=15) 10	$(n=15)$ 4^a	(n=15) 4	$(n=15)$ 1^n	(n=15)	(n=15) 0	(n = 15) $ 0$
•	(n = 15)	(n = 15)	(n=15)	(n=15)	(n = 15)	(n = 13)	(n=9)

Number of patients is shown in parentheses. $^{4}P < 0.05$.





<u>Figure 1</u>. Oral temperature in degrees Celsius versus time after arrival in the postanesthetic recovery area. **A**, group 1 patients treated with cotton blankets; **B**, group 2 patients treated with a forced-air warming system.

(Figure 1A). The regression line in group 2 patients was defined by the formula y = 0.0094x + 34.15 (Figure 1B). The slopes of the two lines were significantly different (P < 0.005).

Discussion

Hypothermia is a common problem in adult postsurgical patients (1–3). Hypothermic patients increase heat production by shivering, a response that may be elicited by an intraoperative decrease in body temperature of as small as 0.3°C (11,12). Shivering increases oxygen consumption by up to 800% above the basal rate (6). Minute ventilation and cardiac output must increase during shivering to meet the ensuing increased tissue demands. Failure to do so results in anaerobic metabolism with progressive metabolic acidosis (1). Patients with preexisting cardiovascular or pulmonary disease may be unable to compensate for such metabolic derangements, and prolonged postoperative hypothermia may thus lead to increased postoperative mortality in such patients (2).

Anesthetic agents interfere with central temperature regulation by lowering the set-point for thermoregulatory shivering in the hypothalamus (13). The conventional explanation for postanesthetic tremor is that on emergence from anesthesia the hypothalamic set-point returns toward baseline. The hypothermic state induced by anesthetic agents combined with intraoperative heat loss secondary to convection and radiation during surgery then triggers thermoregulatory shivering. Recently, Sessler et al. reported that postanesthetic tremor differed from thermoregulatory shivering when analyzed by electromyograms (14). The electromyogram pattern of postanesthetic tremor resembled that of patients with pathologic ankle clonus after spinal cord transection. The authors postulate that spinal reflex hyperactivity secondary to anesthetic-induced depression of cortical inhibition, combined with stimulation of cutaneous cold receptors acting as a trigger, results in postanesthetic tremor. Consistent with this theory is the observation that skin surface warming inhibits postanesthetic tremor (15,16).

The present study supports these conclusions. Patients in group 1 had a significantly (P < 0.05) higher incidence of shivering at both 15 and 45 min

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after admission to the recovery room. The major sources of heat loss during surgery are convection and radiation (17). Radiant heat loss is directly proportional to the difference between patient and ambient temperature; convective heat loss is a function of ambient temperature and the square root of air velocity passing over exposed body surfaces. A forced-air warming system eliminates both these types of heat loss by eliminating the gradient between the patient and the ambient air, and thus prevents further cooling in the recovery room. This, in turn, decreases stimulation of the cutaneous thermoreceptors that trigger postanesthetic shivering (14).

Although the incidence of shivering was significantly greater in group 1 than in group 2, shivering decreased over time in both groups (Table 3). These data support the conclusions of Sessler et al. (14) that residual anesthetic causes spontaneous postanesthetic tremor by spinal reflex activation due to inhibition of descending cortical control. As expired concentrations of anesthetic decrease even further with time, central thermoregulation recovers. If classic thermoregulation accounts for postanesthetic tremor, then shivering would be expected to increase with time in the recovery room as the central set-point progressively returned toward baseline. Application of the forced-air warming system prevents stimulation of cutaneous thermoreceptors and initiation of spinal reflex hyperactivity and may account for the decreased incidence of shivering in group 2.

Patients in group 2 were discharged from the recovery room nearly 1 h sooner than patients in group 1 (99.7 min vs 156.0 min, P < 0.003). Hypothermia decreases the minimal alveolar concentration of anesthetics, potentiates neuromuscular blockade, and slows the metabolism of many drugs (8). Some or all of these factors may have played a role in the earlier discharge of patients in group 2 from the recovery room secondary to their more rapid warming and decreased incidence of shivering.

Patients treated with the forced-air warming system were significantly warmer at each measured interval than were patients given warmed cotton blankets. In addition, the rate of warming was significantly more rapid in the forced-air warming group. Delivery of warm air to the skin not only eliminates the major sources of heat loss but provides passive warming as opposed to the metabolically expensive process of shivering.

In summary, the forced-air warming system re-

sulted in a more rapid rate of warming, a decreased incidence of shivering, and earlier discharge from the recovery room than was found for patients warmed with cotton blankets. This system, in eliminating the two major sources of heat loss in surgical patients (convection and radiation), proved to be both safe and effective. In addition, warming is passive using the forced-air warming system in contrast to the metabolically generated warming that occurs when no external heat source is applied.

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Effect of Combined Infusion of Nitroglycerin and Nicardipine on Femoral-to-Radial Arterial Pressure Gradient After Cardiopulmonary Bypass

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MARUYAMA K, HORIGUCHI R, HASHIMOTO H, OHI Y, OKUDA M, KURIOKA T, KONISHI K, MUNEYUKI M, KUSAGAWA M. Effect of combined infusion of nitroglycerin and nicardipine on femoral-to-radial arterial pressure gradient after cardiopulmonary bypass. Anesth Analg 1990;70:428–32.

Nitrates and calcium channel blockers are frequently administered during cardiac surgery. We simultaneously measured femoral arterial pressure and radial arterial pressure to investigate whether nitrates, in conjunction with calcium channel blockers, would influence the central-to-peripheral arterial pressure gradient. Combined nitroglycerin and nicardipine infusion during cardiac surgery involving coronary artery bypass grafting or valve replacement resulted in a significant increase above baseline levels in the femoral-to-radial arterial pressure gradient at 60 min after cardio-pulmonary bypass. In control patients there was no signif-

icant increase in the femoral-to-radial arterial pressure gradient at 60 min after completion of cardiopulmonary bypass. A subsequent study in patients given nitroglycerin and nicardipine identified that the difference in the systolic arterial pressure between femoral and radial arteries was observed 15, 60, and 120 min after completion of cardiopulmonary bypass. However, there was no difference in the mean arterial pressure between femoral and radial arteries throughout the same period. We conclude that combined infusion of nitroglycerin and nicardipine, a new calcium channel blocker, intensifies the magnitude and duration of the femoral-to-radial arterial pressure gradient after cardiopulmonary bypass.

Key Words: ANESTHESIA, CARDIOVASCULAR—arterial pressures. BLOOD PRESSURE MONITORING, CARDIOPULMONARY BYPASS.

Recent studies during cardiac surgery have demonstrated a significant difference between central and peripheral arterial pressure immediately after cardio-pulmonary bypass (CPB) (1,2). Radial arterial pressure does not reflect central aortic pressure in the immediate postbypass period for 20 min (1,2). Recently, intraoperative administration of nitrates and calcium channel blockers during cardiac surgery has been used to prevent, minimize, and treat myocardial ischemia or coronary artery vasospasm (3–6). Although radial, as compared to central, arterial blood pressure tends to be lower immediately after completion of CPB, the influence of nitroglycerin and nicar-

dipine used during cardiac surgery on this difference has not yet been clarified (7). These drugs might increase the central-to-peripheral arterial pressure difference to such a degree as to be mistaken for a dangerously low (peripheral) pressure. In the present paper, we describe the effect of combined nitroglycerin and nicardipine infusion on radial and femoral arterial pressures during cardiac surgery. The effects of these drugs might also provide information regarding the mechanism of the central-to-peripheral arterial pressure gradient immediately after completion of CPB.

Patients and Methods

Protocol 1: Comparison of Femoral-to-Radial Arterial Pressure Gradient of Patients With and Without Nitroglycerin and Nicardipine

Thirty adult patients undergoing cardiac surgery were studied. Fifteen were undergoing coronary ar-

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tery bypass grafting with combined nitroglycerin and nicardipine infusion (group A; eight men and seven women, aged 41–67 yr [mean \pm sp, 58.3 \pm 7.8]); five were undergoing valve replacement with combined nitroglycerin and nicardipine infusion (group B, two men and three women, aged 51–64 yr [58.8 \pm 8.8]); and 10 were undergoing valve replacement without nitroglycerin and nicardipine administration (group C, five men and five women, aged 30–62 yr [46.8 \pm 8.6]). Patients in groups A and B were chronic users of nitrates and calcium channel blockers. Group B patients had a history of anginal attack. Institutional approval for the study and written informed consent from each patient were obtained before surgery.

Patients were premedicated with morphine hydrochloride (10 mg intramuscularly), droperidol (2.5–5.0 mg) or diazepam (5 mg intramuscularly), and scopolamine sulfate (0.5 mg subcutaneously), all 45 min before induction of anesthesia. Anesthesia was induced with 0.07–0.1 mg/kg fentanyl, followed by 4–6 mg pancuronium with 100% oxygen, with 5-10 mg diazepam on occasion. The trachea was intubated orally after intratracheal injection of 150 mg lidocaine for topical anesthesia. Anesthesia was maintained with 0.2–1.0 mg intravenous fentanyl or 10 mg intravenous diazepam with 100% oxygen or 50% nitrous oxide in oxygen until the start of CPB. Within 5-10 min after the initiation of CPB, 0.5–1.5 mg/kg chlorpromazine and 30 mg/kg methylprednisolone were administered to all patients. There were no differences between groups with the dose of fentanyl, diazepam, or chlorpromazine. The duration of CPB averaged 146 \pm 33 min in group A, 123 \pm 12 in group B, and 126 ± 40 in group C, with no significant differences between groups. Nine of the 15 patients in group A, three of the five patients in group B, and five of the 10 patients in group C required inotropic support (5–10 μ g·kg⁻¹·min⁻¹ dopamine) after CPB. We used the values of the femoral arterial pressure to control blood pressure. There were no patients taking preoperative β -adrenergic receptor blockers. There were no differences in rectal temperature between groups.

In the patients of groups A and B, the combined continuous infusion of nitroglycerin (Nihonkayaku, Japan) at a dose of $0.25\text{--}0.5~\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and nicardipine (Yamanouchi, Japan) at a dose of $0.25\text{--}0.5~\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was started immediately before induction of anesthesia and was continued throughout surgery, including the period of CPB. The radial artery was catheterized percutaneously with a 5.0-cm, 19-gauge Teflon catheter, and the femoral artery was cannulated with a 6.5-cm, 18-gauge Teflon catheter. Each catheter was attached with high-pressure

tubing, an Intraflow continuous flush system, and a Gould P23 transducer to a blood pressure measurement unit, AP610G (Nihon Kohden Co., Japan) or DS-1100 (Fukuda Denshi Co., Japan). The dynamic response of the arterial pressure monitoring system was measured by the flush method as described by Gardner (8). Natural frequency and damping coefficient were 14–17 Hz and 0.43–0.48, respectively. These damping coefficient and natural frequency measurements were in a range able to give adequate dynamic response. A Swan–Ganz catheter was inserted via the right internal jugular vein into the pulmonary artery. Data are given as mean \pm sp.

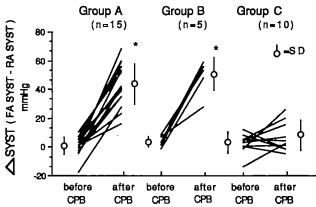
Systolic arterial pressure (SYST), diastolic arterial pressure (DIAST), and mean arterial pressure (MAP) obtained electronically were measured simultaneously from both the femoral artery (FA) and the radial artery (RA). The gradient of systolic arterial pressure between FA and RA was defined as Δ SYST (Δ SYST = FA SYST - RA SYST). The gradient of mean arterial pressure between the FA and RA was defined as Δ MAP (Δ MAP = FA MAP - RA MAP). Cardiac output was measured by the thermodilution technique. Pressures and cardiac output were measured at two times: after induction of anesthesia but before CPB, and 60 min after the completion of CPB.

Protocol 2: Intraoperative Time-Course of Femoral and Radial Arterial Pressures With Nitroglycerin and Nicardipine

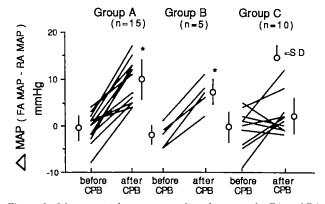
Another set of patients undergoing cardiac surgery with nitroglycerin and nicardipine (partly including group A and B patients, n=14, eight women and six men, 41–64 yr [58.1 ± 8.0]) was studied. The femoral and radial arterial pressures were measured after induction of anesthesia as well as 15, 60, and 120 min after the completion of CPB to investigate the duration of pressure differences in patients given nitroglycerin and nicardipine.

Statistical Analysis

Student's t-test (paired) was used for analysis of intragroup difference. One-way analysis of variance was applied to assess intergroup differences of cardiac output. In protocol 2, in order to detect changes in arterial pressure in each artery during the study, repeated-measures analysis of variance was used followed by the Bonferroni t-test when significant differences were found. Radial and femoral arterial pressures at the same point were compared using



<u>Figure 1</u>. Systolic arterial pressure gradient between the FA and RA. Sixty minutes after completion of CPB, ΔSYST increased significantly above pre-CPB values in groups with nitroglycerin and nicardipine (groups A and B). On the other hand, there was no significant change from pre-CPB values in group C. Abbreviations: CPB, cardiopulmonary bypass; ΔSYST, the systolic pressure gradient between femoral artery and radial artery; FA, femoral artery; RA, radial artery; group A, patients undergoing coronary bypass grafting with combined nitroglycerin and nicardipine infusion; group B, patients undergoing valve replacement with combined nitroglycerin and nicardipine infusion. *Significantly different from pre-CPB value (P < 0.01). Values are mean \pm sp.



<u>Figure 2</u>. Mean arterial pressure gradient between the FA and RA. Sixty minutes after completion of CPB, ΔMAP increased significantly above pre-CPB values in groups with nitroglycerin and nicardipine (groups A and B). On the other hand, there was no significant increase from the pre-CPB value in group C. Abbreviation: ΔMAP, mean arterial pressure gradient between femoral artery and radial artery. For other abbreviations, see Figure 1. *Significantly different from pre-CPB value (P < 0.01). Values are mean \pm sp.

Student's *t*-test. A *P* value of <0.05 was considered to indicate a statistically significant difference.

Results

Pressure gradients between the FA and RA are shown in Figures 1 and 2. Before CPB, Δ SYST was

<u>Table 1</u>. Cardiac Output Before and After Cardiopulmonary Bypass

	n	Before CPB (L/min)	After CPB (L/min)
Group A	15	4.09 ± 1.77	6.53 ± 1.51*
Group B	5	3.04 ± 0.95	6.96 ± 2.64^{a}
Group C	10	3.76 ± 1.86	$6.33 \pm 0.49^{\circ}$

Group A: patients undergoing coronary bypass grafting with combined nitroglycerin and nicardipine infusion; group B: patients undergoing valve replacement with combined nitroglycerin and nicardipine infusion; and group C: patients undergoing valve replacement without combined nitroglycertn and nicardipine infusion.

"Significantly different from values before CPB (P < 0.01).

 1 ± 6 mm Hg (range, -18 to 10 mm Hg) in group A, 3 ± 2 mm Hg (range, -2 to 8 mm Hg) in group B, and -2 ± 7 mm Hg (range, -14 to 12 mm Hg) in group C. Sixty minutes after completion of CPB, Δ SYST increased significantly above its pre-CPB values in groups A and B (group A: 43 ± 15 mm Hg [range, 16-68 mm Hg], group B: 49 ± 12 mm Hg [range, 28-56 mm Hg]). On the other hand, there was no significant increase above the pre-CPB value in group C at 60 min after completion of CPB (mean, 6 ± 10 mm Hg; range, -5 to 26 mm Hg).

Before CPB, Δ MAP was 0 ± 3 mm Hg (range, -8to 4 mm Hg) in group A; -1 ± 1 mm Hg (range, -5to 1 mm Hg) in group B; and 1 ± 4 mm Hg (range, -9to 4 mm Hg) in group C. Sixty minutes after completion of CPB, \(\Delta MAP \) increased significantly above its pre-CPB value in groups A and B (group A: 9 ± 6 mm Hg [range, 4–17 mm Hg]; group B: 7 ± 2 mm Hg [range, 2–11 mm Hg]). On the other hand, there was no significant increase from the pre-CPB value in group C (2 \pm 5 mm Hg [range, -3 to 12 mm Hg]). These results showed that in patients given nitroglycerin and nicardipine, ΔSYST and ΔMAP increased 60 min after completion of CPB; no significant increase was observed in patients not given nitroglycerin and nicardipine. There was no change from the pre-CPB value in the gradient of diastolic pressure between the FA and RA in all three groups. Cardiac output after completion of CPB increased significantly in all three groups (Table 1). There was no difference among groups in the values before and after CPB, respectively.

The time-course of changes of systolic and mean arterial pressures measured in both femoral and radial arteries in patients with nitroglycerin and nicardipine is shown in Figures 3 and 4. Femoral systolic arterial pressure did not change throughout the course of the study. Values of radial systolic arterial pressure 15 and 60 min after completion of CPB were significantly lower than baseline values. Femoral mean arterial pressure 15 min after completion of

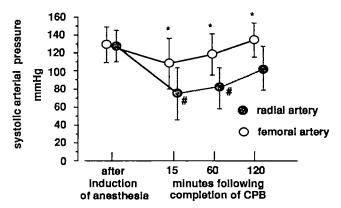


Figure 3. Time-course of changes of systolic arterial pressure in both FA and RA in patients with nitroglycerin and nicardipine. In femoral systolic arterial pressure, there was no change throughout the study. In radial systolic arterial pressure, values at 15 and 60 min after completion of CPB were significantly lower than baseline value (repeated-measures analysis of variance followed by the Bonferroni t-test). There was no difference between femoral and radial arteries in the values of systolic arterial pressure after induction of anesthesia. A significant pressure difference between femoral and radial arteries was observed in systolic values at 15, 60, and 120 min after completion of CPB. The radial and femoral arterial pressures were compared at each time point using Student's t-test. n=14. Values are mean \pm sp. *Significantly different from the value of radial artery at the same time point (P < 0.05). #Significantly different from the baseline value (P < 0.05).

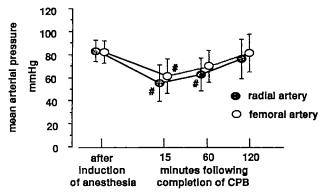


Figure 4. Time-course of changes of mean arterial pressure in both FA and RA in patients with nitroglycerin and nicardipine. In femoral mean arterial pressure, the value at 15 min after completion of CPB was significantly lower than baseline value. In radial mean arterial pressure, the values at 15 and 60 min after completion of CPB were significantly lower than baseline value (repeated-measures analysis of variance followed by the Bonferroni t-test). In the mean arterial pressure, there was no difference between femoral and radial arteries throughout the study (Student's t-test). n = 14. Values are mean \pm sp. #Significantly different from the baseline value (P < 0.05).

CPB was significantly below baseline values. Radial mean arterial pressures at 15 and 60 min after completion of CPB were significantly lower than baseline value. There was no difference between femoral and radial arterial pressures of either systolic or mean arterial pressure after induction of anesthesia. A significant pressure difference between femoral and

radial arteries was observed in systolic values at 15, 60, and 120 min after completion of CPB. Mean arterial pressure was not significantly different in femoral and radial arteries throughout the study.

Discussion

This study demonstrates that combined nitroglycerin and nicardipine infusion during cardiac surgery involving coronary artery bypass grafting or valve replacement results in an increase in femoral-to-radial arterial pressure gradient 60 min after completion of CPB to significantly above prebypass values. The significant differences between systolic arterial pressures in the femoral and radial arteries were observed 15, 60, and 120 min after completion of CPB. But the differences between mean arterial pressures in the femoral and radial arteries were not apparent throughout the study. On the other hand, without nitroglycerin and nicardipine, there was no significant increase in femoral-to-radial arterial pressure gradient 60 min after completion of CPB. This suggests that during cardiac surgery with nitroglycerin and nicardipine infusion, systolic arterial pressure might be underestimated after completion of CPB when measured at the RA as compared with the FA, resulting in possibly inappropriate overadministration of inotropic and vasoactive drugs given to control blood pressure.

We used a 19-gauge catheter for the RA and an 18-gauge catheter for the FA. Any changes in the femoral-to-radial arterial gradient could at least be a reflection of the difference in catheter size. The damping coefficient and natural frequency from both the radial and femoral arteries were in range to give adequate dynamic response (8). And the baseline arterial pressures were similar between the RA and the FA.

The pressure gradient between peripheral and central arteries immediately after completion of CPB was first described by Stern et al. (1). They measured direct central aortic and radial arterial pressures during open heart surgery. Their results showed that the systolic aortic pressure is greater than the radial arterial pressure over a period of 20 min after completion of CPB. Gravlee et al. have also shown that the central-to-peripheral pressure gradients present after completion of CPB were resolved within 10–20 min (2). Sixty minutes after completion of CPB, radial arterial pressure is assumed generally to reflect central aortic pressure (1,2). In view of these previous studies, we decided to compare patients with and without nitroglycerin and nicardipine at 60 min after

completion of CPB. Results obtained 60 min after completion of CPB in group C without nitroglycerin and nicardipine showed no significant difference between femoral and radial arterial pressures. On the other hand, patients given nitroglycerin and nicardipine had significant increases in the pressure difference between the femoral and radial arterial pressures at the same time point. Stern et al. suggest that this gradient may be due to lowered forearm vascular resistance after CPB (1). Pauca et al. also noted a decrease in peripheral vascular resistance of varying degrees after completion of CPB (7). Our results show that at least the combined infusion of nitroglycerin and nicardipine intensified the degree and duration of the femoral and radial arterial pressure gradient after completion of CPB. This may support vasodilation as the explanation for these findings, because these drugs have vasodilatory effects. Further investigation will be necessary for the applicability of this result to other vasodilators.

There is a possibility that chronic users of nitrates and calcium channel blockers have altered peripheral vascular tone. Thus, there is the possibility that the chronic use of these agents, rather than the infusion of these agents during cardiac surgery, are responsible for the effects on arterial pressure gradients. Because this study did not include patients who were chronic users of nitrates and calcium channel blockers but who did not receive drug infusion during the surgery, we cannot eliminate this possibility.

We conclude that combined infusion of nitroglycerin and nicardipine, a new calcium channel blocker, intensifies the magnitude and duration of the femoral-to-radial arterial pressure gradient after completion of CPB, given at least to the chronic user of these drugs.

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Review Article

Pro- and Anticonvulsant Effects of Anesthetics (Part II)

Paul A. Modica, MD, Rene Tempelhoff, MD, and Paul F. White, PhD, MD

Key Words: ANTICONVULSANTS. BRAIN, PROAND ANTICONVULSANTS. COMPLICATIONS, CONVULSIONS. TOXICITY, CONVULSIONS.

Part I

Introduction

Inhalation anesthetics

Volatile agents

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Isoflurane

Investigational volatile agents

Nitrous oxide

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Opioid (narcotic) analgesics

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Morphine

Fentanyl and its analogues

Summary

Part II

Introduction

Intravenous anesthetics

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Ketamine

Propofol

Local anesthetics

Anesthetic adjuvants

Muscle relaxants

Anticholinesterases

Anticholinergics

Summary

Part I of this review article appeared in the previous issue (Anesth Analg 1990;70:303–15).

Anesthetic, analgesic, and muscle relaxant drugs produce varying effects on electroencephalographic (EEG) activity. In the first part of this review article, we described the pro- and anticonvulsant effects of the inhaled anesthetics and the opioid (narcotic) analgesics. Variations in drug dosages, methods of drug administration, and EEG documentation, as well as differences in the patient populations, contribute to the contrasting effects of these drugs on central nervous system (CNS) activity.

In the second part of this pharmacologic review, we describe the reported EEG effects of the sedative-hypnotic compounds (including the barbiturates, etomidate, benzodiazepines, ketamine, and propofol), local anesthetics, muscle relaxants, anticholinesterases, and anticholinergics. The evidence for druginduced changes in EEG activity will be critically reviewed with respect to the patient population (i.e., epileptic vs nonepileptic), documentation (i.e., EEG vs clinical signs), and methodology (i.e., surface vs depth electrodes).

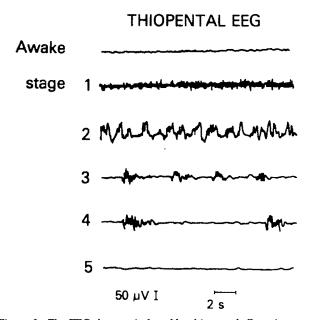
Intravenous Anesthetics

Sedative-Hypnotics

Barbiturates. In patients without a history of seizure disorder, low doses of thiopental and methohexital can cause activation of the EEG producing 15–30-Hz waves. With increasing doses of these sedative-hypnotic drugs, slower waveforms of higher amplitude appear that progress to burst suppression at high doses (157–161) (Figure 3). Electroencephalographic or clinical seizure activity has not been reported in nonepileptic patients treated with these ultrashort-acting barbiturates (Table 5). However, excitatory phenomena such as abnormal muscle movements, hiccoughing, and tremor may occur with both thiopental and methohexital. These excitatory side effects are more common with methohexital (64,162,163).

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Figure 3. The EEG changes induced by thiopental. Consciousness is lost early in stage 1. Stages 2 and 3 represent surgical anesthesia. Barbiturate coma is indicated in stages 4 and 5. (From Hudson R, Stanski D, Saidman L, Meathe E. A model for studying depth of anesthesia and acute tolerance to thiopental. Anesthesiology 1983; 59:301–8, with permission.)

The tendency of methohexital to provoke convulsions during intravenous induction (0.5–1.0 mg/kg) in patients with a history of epilepsy is well known (164-166) (Table 5). Seizure activity has also been reported after intramuscular (10 mg/kg) or rectal (25 mg/kg) methohexital administration in children with temporal lobe epilepsy (167). Low-dose (≤0.5 mg/kg) methohexital has proved valuable in the activation of cortical EEG seizure discharges in patients with psychomotor (temporal lobe) epilepsy (11,12,168). This technique has been used during intraoperative electrocorticography to activate epileptic foci during temporal lobectomy (12). Methohexital also adds valuable negative EEG evidence in cases of suspected behavior disorders (11). Only nonspecific EEG effects have been reported after methohexital administration to patients with a history of generalized seizure disorders (11,159).

In three epileptic patients, thiopental activated brief periods (<7 s) of bilateral atypical and polyspike waves during induction, which were not associated with observable seizures (63). The brief periods of spike waves detected in this report were most likely associated with "light" levels of thiopental anesthesia, an accepted method for eliciting convulsive tendencies (25,53,169). Similar intermittent spiking activity also was detected with depth electrodes after low doses of thiopental (<1.5 mg/kg, IV) administered to patients with temporal lobe epilepsy (53). Furthermore, larger doses of thiopental (>5 mg/kg, IV)

produced EEG patterns in these epileptics, which closely resembled the changes produced by the drug in normal patients (16,25) (Table 5). In patients with psychomotor epilepsy in whom methohexital produced EEG and clinical seizure activity, subsequent administration of thiopental did not (12).

In humans, thiopental has well-known anticonvulsant properties (Table 6). After an initial intravenous injection of 250–1000 mg given slowly until cessation of seizures, continuous thiopental infusions (80–120 mg/h) for as long as 13 days have been used successfully in intubated and ventilated patients to control status epilepticus refractory to more conventional anticonvulsant drugs (170,171). The infusions were titrated to produce a burst suppression EEG pattern. Interestingly, the seizures did not recur after discontinuation of the infusion.

In one series of more than 900 patients with unspecified types of epilepsy, the frequency of epileptiform activity during anesthetic induction with methohexital was much less when compared with the previous sleep and awake EEGs of these epileptics (53). Methohexital has never been demonstrated to provoke either EEG or clinical seizure activity in patients with generalized convulsive disorders (11,159). Thus, although the epileptogenic effects of methohexital in patients with psychomotor epilepsy are well established, the ultrashort-acting barbiturates are predominantly potent anticonvulsant agents.

Etomidate. The EEG patterns produced by etomidate are similar to those associated with thiopental (144,157,172). The main EEG difference between equihypnotic doses of etomidate (0.3 mg/kg) and thiopental (3.5 mg/kg) is a lack of beta activity during "light stages" of etomidate anesthesia (157). Higher doses of etomidate produce burst suppression patterns analogous to the barbiturate compounds (157,172). Involuntary myoclonic movements are common during induction of anesthesia with etomidate, and occasionally resemble generalized convulsive seizures (145,157,173). This myoclonus can persist into the recovery period (144-146). There have also been reports of generalized or focal convulsivelike movements occurring in ventilated patients receiving long-term etomidate infusions for sedation (174,175). However, EEG correlation was not performed and none of these patients had a previous or subsequent history of epilepsy. In one of these reports (175), the involuntary motor activity was suppressed with higher doses of etomidate.

Whether these convulsivelike movements associated with etomidate administration in nonepileptic

Table 5. Proconvulsant Effects of Sedative-Hypnotics and Local Anesthetics in Humans

		Seiz docume		Type of EEG	
Agent	Population	Clinical report	EEG study	electrodes used in study	Reference
Thiopental	Nonepileptic Epileptic	<u>-</u>	<u>-</u> -	Surface Surface/depth	157, 158, 161 16, 25, 63
Methohexital	Nonepileptic Epileptic	 +	 +	Surface Surface	159, 160, 168 11, 12, 164
Etomidate	Nonepileptic Epileptic	++	++	Surface Surface/depth	174–176 53, 176, 180, 181
Benzodiazepines	Nonepileptic Epileptic	_ +	- +	Surface Surface	186, 187 188–190
Ketamine	Nonepileptic Epileptic	++	- +	Surface Surface/depth	140, 186, 197–204 16, 63
Propofol	Nonepileptic Epileptic	-	- +	Surface Surface	214, 215 216
Local anesthetics	Nonepileptic Epileptic	++	++	Surface Depth	221–225, 230, 231 220

^{+,} presence of seizures; -, absence of seizures; EEG, electroencephalographic.

<u>Table 6</u>. Anticonvulsant Effects of Sedative-Hypnotics and <u>Local Anesthetics in Humans</u>

	Anticonvulsant documentation		Type of EEG	
Agent	Clinical report	EEG study	used in study	Reference
Thiopental	+	+	Surface	170, 171
Methohexital	N/A	N/A		
Etomidate	+	+	Surface	184, 185
Benzodiazepines	+	+	Surface	191-193
Ketamine	+	N/A		9, 10, 212
Propofol	+	N/A		217
Local anesthetics	+	N/A		238-241

 ^{+,} successful termination of status epilepticus reported; EEG, electroencephalographic; N/A, information not available.

patients represent seizure activity is unclear. Surface EEG studies performed in patients without a history of epilepsy treated with etomidate have not revealed spiking activity during these myoclonic movements (144,157,172). In some of these patients, simultaneous electromyographic, plantar reflex, and soleus muscle M-wave/H-reflex recordings indicated that the etomidate-induced myoclonus was of spinal (nonepileptic) origin (144). Conversely, in one report of more than 30 nonepileptic patients undergoing open heart surgery, surface EEG monitoring demonstrated generalized epileptiform activity in approximately 20% of the cases after etomidate induction (176) (Table 5). However, no myoclonic or convulsivelike movements were reported during these episodes of apparent EEG seizure activity.

Etomidate infusion produces a 2- to 12-fold increase in the amplitude of median (177) and posterior tibial (178) nerve somatosensory evoked potentials. The increased amplitude may represent an alteration of the balance of inhibitory and excitatory influences in the thalamocortical tracts (178,179). This suggests that etomidate could produce myoclonus either by blockade of inhibition or enhancement of excitability in these subcortical CNS tracts. Higher plasma levels of etomidate may prevent myoclonic movements by depressing both inhibitory and excitatory neuronal firing (175).

It is also possible that the convulsivelike movements associated with etomidate could be due to subcortical seizure activity. Depth electrode investigations during etomidate administration have been performed in two patients, both suffering from temporal lobe epilepsy (180). In these two cases, etomidate (0.2–0.3 mg/kg, IV) induced an electrographic seizure originating from the known subcortical seizure foci. Because of concomitant nondepolarizing muscle relaxant administration, it is unknown whether or not myoclonic or convulsivelike movements would have been associated with this subcortical seizure activity.

Surface EEG studies in patients with a history of epilepsy have further documented the proconvulsant effects of etomidate (53,176,181) (Table 5). In 39 epileptic patients, convulsionlike potentials were recorded within 30 s after anesthetic induction with etomidate and occurred more frequently than during sleep or awake EEG testing (53). Interestingly, no

myoclonic or convulsivelike movements were reported during these episodes of etomidate-induced EEG seizure activity. In patients undergoing electrocorticography before temporal lobectomy for intractable complex partial seizure disorders, etomidate (0.2–0.3 mg/kg, IV) administered during or within 10 min of discontinuation of 50%-70% nitrous oxide (N₂O) activated EEG epileptiform activity in more than 75% of the patients (176,181). The well-known EEG activating effects of N2O cannot be ruled out as an additive factor in these two reports. Furthermore, correlation between EEG and clinical seizure activity may have been prevented by concomitant nondepolarizing neuromuscular blockade. Interestingly, after etomidate induction, one of the epileptics studied exhibited grand mal convulsivelike movements before the institution of muscle relaxation and EEG monitoring (176). Thus, it was unclear whether the clinical seizure observed in this case was due to cortical/subcortical epileptiform activity or exaggerated nonepileptic myoclonus.

Etomidate appears to possess anticonvulsant properties in both humans and animals. The drug increased the threshold for both narcotic-induced EEG seizures in dogs (8) and bicuculline-induced seizures in rats (182). In amygdaloid kindled rats, etomidate suppressed seizure activity (183). In humans, successful termination of EEG-documented status epilepticus has been demonstrated after etomidate administration (184,185) (Table 6).

Overall, etomidate has both pro- and anticonvulsant effects on EEG. In view of the finding that higher doses of the drug suppress low dose-induced involuntary motor activity, it appears that the dose and rate of etomidate administration probably determines which of its contrasting effects on the seizure threshold will occur in a particular clinical setting. Furthermore, additional studies of the EEG effects of progressively higher doses of etomidate (without concomitant muscle relaxation) are required to determine if etomidate-induced myoclonus is of epileptic or nonepileptic origin.

Benzodiazepines. After diazepam (10–20 mg, IV) an increase in EEG amplitude can be seen in the beta band between 12 and 22 Hz. There is also a reduction in alpha activity and transient increases in amplitude in the delta/theta band (186,187). The increased activity in the beta range is probably related to the major clinical effect of the benzodiazepines (e.g., sedation, amnesia). The percentage of beta activity appears to correlate with diazepam blood levels (187). Electroencephalographic or clinical seizure activity has not been reported in nonepileptic patients treated with benzodiazepines (Table 5).

The occurrence of status epilepticus has been reported with diazepam (188–190). Although observed in one child with petit mal seizures (189), this paradoxical effect of diazepam usually occurs in patients with Lennox–Gastaut syndrome, a form of secondary generalized epilepsy (188,190). In these epileptics, benzodiazepines can induce brief episodes of EEG and clinical seizure activity (Table 5).

In general, the benzodiazepines used in anesthetic practice possess potent anticonvulsant properties in both humans and animals. In humans, diazepam (191) and lorazepam (192,193) have been widely used to terminate episodes of status epilepticus (Table 6). Suppression of EEG seizure activity has been demonstrated after intravenous (191), intramuscular (194), and rectal (195) routes of administration. The absorption and efficacy of rectal diazepam appears to be analogous to or superior to that of the intramuscular route (195). Midazolam (15 mg, IM) is as effective as diazepam (20 mg, IV) in abolishing interictal spikes (194). Thus, although intravenous diazepam (or midazolam) is often regarded as the drug of choice in the emergency therapy of generalized seizure disorders, it appears that both intramuscular midazolam and rectal diazepam are acceptable alternative routes of administration in situations where it is not possible to establish intravenous access (194). Not surprisingly, the duration of antiseizure activity after lorazepam (4-8 mg, IV) is longer than that achieved with intravenous diazepam (193). Because of its high affinity for the benzodiazepine receptor (196), repetitive doses of lorazepam are rarely required for continuing control of seizures. Overall, the benzodiazepines are effective in controlling status epilepticus occurring in more than 90% of patients with generalized seizure disorders. Also, they are effective in approximately 60% of cases of status epilepticus occurring in partial epilepsy (188).

Ketamine. In patients without a history of seizure disorder, cortical EEG recordings 1-2 min after ketamine (1-3 mg/kg, IV) are characterized by the initial appearance of fast beta activity at 30-40 Hz, which is followed by moderate-voltage theta activity mixed with high-voltage delta waves recurring at 3-4-s intervals (140,186). Higher doses of ketamine (>2 mg/kg, IV) produce a burst suppression EEG pattern. The 30-40-Hz activity is maximal frontally and tends to persist even when the theta and delta activity appears. The variety of EEG patterns produced by racemic ketamine have been attributed to differences between the drug's two optical isomers with regard to their anesthetic potency and EEG effects (Figure 4) (197,198). When the more potent S(+) isomer of ketamine is infused to produce a state of clinical

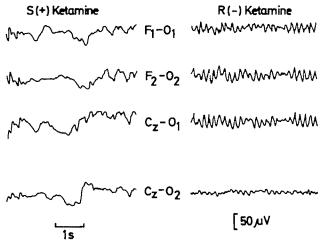


Figure 4. A four-lead EEG pattern demonstrating the maximal slowing during or immediately after the infusion of S(+) ketamine or the R(-) isomer. (From White PF, Schuttler J, Shafer A, Stanski DR, Horai Y, Trevor AJ. Comparative pharmacology of the ketamine isomers: studies in volunteers. Br J Anaesth 1985;57:197–203, with permission.)

anesthesia, a progressive decrease in EEG amplitude and frequency occurs, followed by intermittent high-amplitude polymorphic delta activity. In contrast, larger doses of the less potent R(-) ketamine are unable to produce the same degree of EEG suppression.

Electroencephalographic seizure activity has not been reported in nonepileptic patients during ketamine administration. However, the occurrence of myoclonic and seizurelike motor activity has been observed clinically in nonepileptic children and adults after intravenous (2 mg/kg) or intramuscular (10–12 mg/kg) ketamine (199–203) (Table 5). These movements were noted soon after induction (199) and later after additional incremental doses (202–204). Unfortunately, simultaneous EEG recordings were not available. In four nonepileptic asthmatics receiving aminophylline, extensor-type seizures occurred within minutes after induction with ketamine (1–2 mg/kg, IV) (205). In mice, aminophylline appears to decrease the seizure threshold for ketamine (205).

Although surface EEG recordings have not revealed seizure activity in nonepileptic patients treated with ketamine, it is conceivable that the convulsivelike movements observed in these nonepileptic patients could be due to subcortical seizure activity. After ketamine administration to normal cats, subcortical seizure activity has been recorded from chronically implanted depth electrodes. In these cats, ketamine produced intermittent hypersynchrony with spiking activity in the limbic system, which subsequently spread to subcortical nuclei and the neocortex (6,206,207). This subcortical and cortical EEG seizure activity was associated with excita-

tion, catalepsy, muscle twitching, and bizarre posturing. Furthermore, ketamine-induced subcortical activation was implicated as the cause of severe myoclonus in infants with myoclonic encephalopathy (Kinsborne syndrome) (208). In view of these findings, it is possible that depth electrode EEG recordings in nonepileptic patients treated with ketamine would detect subcortical seizure activity with or without convulsivelike movements.

It is well-established that ketamine will activate epileptogenic foci in patients with known seizure disorders (16,63) (Table 5). In nine epileptics with cortical and depth electrode implants, Ferrer-Allado et al. (16) demonstrated seizure activity originating subcortically in the limbic and thalamic areas after ketamine (2-4 mg/kg, IV) (Figure 5). The seizures were accompanied by tonic-clonic activity in half the patients; however, they were not always manifested on the surface EEG recordings. Furthermore, administration of a smaller dose of ketamine (0.5–1.0 mg/kg, IV) produced only subcortical seizure activity (without loss of consciousness) and/or increased frequency in the 15-50-Hz range, similar to that demonstrated in nonepileptics. Thus, it appears that ≥2 mg/kg of intravenous ketamine is required to activate either ' cortical EEG or clinical seizure activity in epileptics. Celesia et al. (209) in a study of 26 epileptic patients given ketamine (0.5-2.0 mg/kg, IV) did not report any cortical or clinical seizure activity with surface EEG monitoring. Conversely, intermittent paroxysmal epileptiform discharges were recorded on surface EEG in six of eight epileptic patients given ketamine (4-10 mg/kg, IM, followed by 1-20 mg/kg, IV, in divided doses) (63). Three of these patients manifested clinical convulsions with increases in seizure activity for up to 3 mo after ketamine administration. Subcortical withdrawal seizures have been reported for up to 5 days after discontinuation of ketamine in rats that were chronically exposed to the drug (210).

Ketamine appears to possess anticonvulsant properties in both humans and animals. In mice, ketamine prevented both electrical and pentylenetetrazolinduced seizures (211), whereas in rats, the drug terminated 3-mercaptopropionic acid-induced seizures (84). Corssen et al. (212) suggested that ketamine may have anticonvulsant properties because it effectively terminated tonic-clonic convulsions in two patients (Table 6). Fisher (9) reported that ketamine (5-20 mg/kg, IM) produced cessation of grand mal seizure movements in two children with a history of multiple admissions for resistant status epilepticus. Furthermore, in three children with febrile convulsions unresponsive to conventional antiepileptic therapy, ketamine (1-4 mg/kg, IV, and 2.5 mg/kg, IM, on separate occasions) rapidly terminated clinical seizure

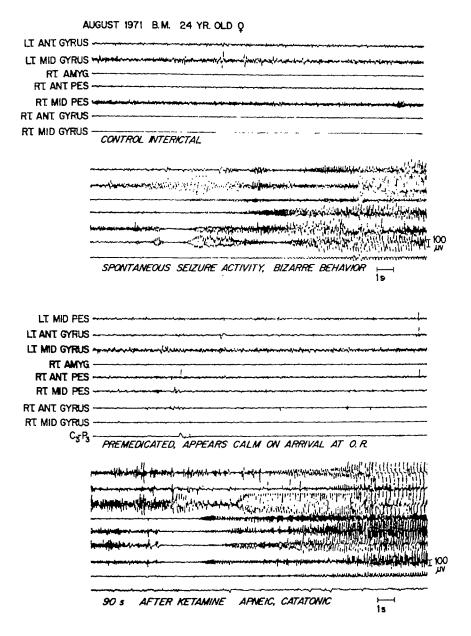


Figure 5. Electroencephalographic changes after ketamine (2–4 mg/kg, IV). The EEG shows the onset of electrical seizure activity in the left mid gyrus and its spread to other limbic and thalamic areas. The cortical electrodes (C₃-P₃) do not reflect seizure activity. (From Ferrer-Allado T, Brechner VL, Dymond A, Cozen H, Crandall P. Ketamine-induced electroconvulsive phenomena in human limbic and thalamic regions. Anesthesiology 1973;38:333–44, with permission.)

activity (10). In these children, ketamine's rapid onset of anticonvulsant action via the intramuscular route appeared to be a potential advantage over conventional intravenous anticonvulsants in treating status epilepticus. Unfortunately, in all of these reports, simultaneous EEG recordings were not available to further support these apparent anticonvulsant actions for ketamine. In addition, the available evidence indicates that ketamine possesses primarily potent cerebral stimulatory properties, especially in patients with seizure disorders in whom the drug activates subcortical seizure activity.

Propofol. Propofol is a newer intravenous anesthetic that can be used for both induction and maintenance of general anesthesia. In humans, propofol

has been reported to produce excitatory activity (e.g., movements, myoclonus, muscle tremors, and hiccoughs) during induction of anesthesia (213). Although the incidence of the excitatory effects with propofol may be higher than with thiopental, the incidence appears to be less than with either methohexital or etomidate (213). Whether these abnormal movements associated with propofol induction represent true seizure activity or merely nonepileptic myoclonia is unknown, as simultaneous EEG recordings have not been performed during these excitatory side effects. Unlike etomidate (174,175) prolonged seizurelike excitatory movements during or after continuous infusion of propofol have not been observed.

In patients without a history of seizure disorder, cortical EEG changes similar to those produced by thiopental were demonstrated after propofol (2 mg/kg, IV) (214,215). Neither epileptiform activity nor excitatory movements were reported (Table 5). However, in three patients with a history of intractable temporal lobe epilepsy, Hodkinson et al. (216) described activation of epileptogenic foci after a bolus of propofol (2 mg/kg, IV). In each case, electrocorticography revealed frequent discharges of spikes, polyspikes, and spike and wave complexes 20–30 s after injection, continuing for up to 7 min. No patient exhibited excitatory motor effects and the EEG seizure activity ceased spontaneously.

Propofol appears to possess anticonvulsant properties clinically. However, there is no EEG documentation of this effect (Table 6). In a 21-yr-old woman with refractory status epilepticus caused by viral encephalitis, Wood et al. (217) reported that a single bolus of propofol (100 mg, IV) completely suppressed clinical seizure activity. After this, a continuous propofol infusion at 5–7 mg·kg⁻¹·h⁻¹ continued to control her convulsions for 18 days. However, her seizures recurred whenever the infusion was discontinued. In two reports of patients with depressive disorders undergoing electroconvulsive therapy, the mean clinical seizure duration was significantly reduced after propofol (1.3–1.5 mg/kg, IV) compared with methohexital (1 mg/kg, IV) (218,219).

Local Anesthetics

Local anesthetics are well-known convulsants in patients with and without a history of seizure disorder (220,221) (Table 5). Clonic or tonic-clonic activity (64) has occurred after the administration of local anesthetics via the intravenous (220–222), epidural (223,224), or peripheral nerve block (225) routes. Local anesthetic-induced convulsions have not been reported after subarachnoid administration (226–228). High blood levels result from accidental intravascular injection, accumulation after repeated injections, and rapid systemic absorption from a highly vascular area (229). Thus, seizures may be either immediate or delayed after local anesthetic administration.

Surface EEG recordings have not correlated well with the preconvulsive signs and symptoms of local anesthetic toxicity (64,229). Abnormal preseizure EEG activity was not found in humans after the production of preconvulsive signs and symptoms of toxicity by a variety of local anesthetic compounds (222,230,231). The onset of cortical EEG seizure activity was simultaneous with tonic-clonic muscle activity. In contrast, depth electrode EEG recordings in

monkeys treated with lidocaine have revealed a characteristic preconvulsive pattern of diffuse slowing and irregular appearance of large spikes leading directly into generalized seizure activity (232). However, similar to the findings for lidocaine in humans, mepivacaine, bupivacaine, and etidocaine do not consistently produce distinctive preconvulsive EEG changes in animals (229,232,233).

Depth electrode EEG studies in both animals (232,234,235) and epileptic patients (220) have revealed a seizure focus in the limbic system (amygdala, hippocampus) after the administration of local anesthetics. Ablation of the amygdala has also been reported to prevent local anesthetic-induced seizures (64). In rats (236), selective metabolic activation of the limbic system has been demonstrated during lidocaine-induced preseizure activity. These findings support a subcortical origin for local anesthetic-induced seizures and suggest that the preconvulsive signs and symptoms of CNS toxicity in humans may be manifestations of psychomotor seizures (64,237).

Local anesthetics have also been demonstrated to possess anticonvulsant properties in both humans and animals. In general, the anticonvulsant activity of local anesthetic agents occurs at subtoxic blood levels (64,229). In cats in which seizures were produced by intracortical penicillin, a marked anticonvulsant effect was noted at lidocaine blood levels of $<4.0 \mu g/mL$ (229). Blood levels $>4.5 \mu g/mL$ produced signs of cortical irritability, with seizure activity at levels >7.5 μg/mL. In humans, subtoxic doses of lidocaine (1–2 mg/kg, IV), followed by an infusion of 1–3 mg·kg $^{-1}$ · h⁻¹, have been used to terminate status epilepticus (238–241) (Table 6). In patients undergoing electroconvulsive therapy, investigators (242,243) have found that prior administration of lidocaine (or procaine) prevents and/or reduces the duration of electrically induced seizures. In one of these studies (242), after induction of anesthesia with thiopental (4 mg/kg, IV) progressively higher doses of lidocaine (1-11.2 mg/kg, IV) failed to produce seizure activity and were associated with progressively shorter durations of electrically induced convulsions. Furthermore, a lidocaine dose of 16.5 mg/kg, IV (which produced tonic-clonic convulsions in 50% of the patients) prevented electroshock-induced seizures. Unfortunately, none of these studies regarding the anticonvulsant effects of local anesthetics had the benefit of simultaneous EEG documentation.

Local anesthetics can possess both proconvulsant and anticonvulsant properties because of their membrane-stabilizing effects (244). Although local anesthetics generally inhibit neuronal activity, it appears that excitatory pathways are more resistant than inhibitory pathways (64,229,242,245). Thus, at subtoxic doses, local anesthetics can act as anticonvulsants, sedatives, and analgesics (238,246,247). At higher drug concentrations, resistant unopposed excitatory pathways can cause frank convulsions. Ultimately, with further increases in local anesthetic blood levels all pathways are inhibited, resulting in a generalized state of CNS depression (64,229,234).

Anesthetic Adjuvants

Muscle Relaxants

In humans, none of the muscle relaxants used in clinical anesthesia have been reported to cause either EEG or clinical seizure activity. However, at high concentrations, the primary metabolite of atracurium, laudanosine, can produce EEG and clinical seizure activity in animals (248-250). In anephric patients, short-term infusion of attracurium (3–5 $\mu g \cdot kg^{-1}$. min⁻¹) for renal transplantation produced maximum laudanosine blood levels of 0.3–1.0 μ g/mL (251). No intraoperative EEG changes or postoperative seizures were associated with these laudanosine concentrations. However, chronic infusion of atracurium (10-15 μ g·kg⁻¹·min⁻¹) to renally impaired patients in the intensive care unit was associated with laudanosine concentrations as high as 5.1 µg/mL (252), blood levels shown to produce convulsions in rabbits (249). Significantly higher laudanosine concentrations (>17 μg/mL) are required to induce seizures in dogs (248,249). Thus, although it appears that laudanosine levels during surgery are of little (if any) clinical concern, additional studies regarding the CNS effects of long-term atracurium infusions are needed, especially in patients with hepatic failure in whom the half-life of laudanosine is significantly prolonged (253).

In animals, succinylcholine applied topically to the cerebral cortex produced intense EEG stimulation and seizure activity that was believed to be due to direct depolarization of neurons (254). In both humans (255,256) and animals (257,258) anesthetized with halothane, intravenous succinylcholine produced EEG arousal that was associated with significant increases in cerebral blood flow and intracranial pressure. Prior administration of large doses of nondepolarizing muscle relaxants prevented both the EEG activation and intracranial pressure increases induced by intravenous succinylcholine, whereas smaller defasciculating doses had no effect (255,258). As little (if any) of the drug crosses the blood-brain barrier, the EEG arousal with increases in cerebral blood flow/intracranial pressure after intravenous succinylcholine is most likely related to succinylcholine-induced increases in afferent muscle spindle activity and to increases in Paco₂ generated by increased muscle carbon dioxide (CO₂) production (258). In addition, the lack of EEG activation after succinylcholine injection in dogs with disrupted blood-brain barriers (259) further supports this hypothesis and indicates that intravenous succinylcholine does not possess proconvulsant properties.

Usubiaga et al. (260) reported that succinylcholine terminated procaine- and lidocaine-induced muscle seizure activity in humans, but did not affect the duration or pattern of EEG seizure activity. In monkeys, prior administration of gallamine increased the lidocaine EEG convulsive threshold (229). In humans, none of the muscle relaxants used in clinical anesthesia have been reported to possess anticonvulsant properties.

Anticholinesterases

None of the cholinesterase inhibitors (CHEIs) used in clinical anesthesia have been reported to cause EEG or clinical seizure activity in humans. However, acetylcholine is an important component of seizure activity (261). In contrast to the postictal state, brain acetylcholine levels and cerebrospinal fluid turnover increase during seizures. In animals monitored with depth electrodes (262), CHEIs induced cortical and/or subcortical EEG seizure activity. These drugs also lower the threshold for strychnine- and pentylenetetrazol-induced convulsions (261).

In humans, physostigmine appears to reverse CNS depression by increasing central cholinergic activity (263). Its tertiary amine structure allows it to more freely cross the blood-brain barrier. Physostigmine can reverse scopolamine-induced sedation by reversing the acetylcholine depletion (264). For drugs such as diazepam (265), which cause sedation via noncholinergic pathways (e.g., GABAnergic mechanisms), physostigmine-induced central cholinergic activation may produce awakening because of a generalized "arousal" effect (263). This CNS "arousal" effect of physostigmine has been noted on EEG. In both dogs (266) and humans (263) anesthetized with halothane, clinical doses of physostigmine (0.3 mg/ kg, IV) shifted EEG activity from a low-frequency, high-amplitude pattern characteristic of anesthesia, to a higher frequency, lower amplitude awake-type pattern. Physostigmine also reverses the CNS excitation associated with the central anticholinergic syndrome produced by atropine and scopolamine (267,268). The underlying mechanism of these paradoxical effects for both physostigmine and anticholinergic agents is unclear.

In humans, none of the CHEIs used in clinical anesthesia have been reported to possess anticonvulsant properties. In cats, physostigmine reversed a scopolamine-induced increase in enflurane EEG seizure activity (26). These unexpected effects probably involve noncholinergic pathways (269). In clinically relevant doses, none of the CHEIs used in anesthetic practice would be expected to have significant effects on the seizure threshold in humans.

Anticholinergics

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Based on their central cholinergic inhibitory actions, a sedative effect would be expected after clinical doses of the tertiary amine anticholinergic drugs. However, both atropine and scopolamine can produce unexpected CNS excitation and delirium (267,268). Although the precise mechanism of these excitatory effects is not known, it may involve central non-cholinergic antagonist actions (270) and/or a paradoxical activation of nicotinic receptors in the brain (271). These CNS excitatory effects have not occurred with the quaternary amine compound, glycopyrrolate.

Because the central cholinergic system appears to be an important component in generating seizure activity, anticholinergic drugs with tertiary amine structures would be expected to possess anticonvulsant properties. When given alone, clinical doses of atropine (0.5 mg, IV), which can cause drowsiness, typically produce mild increases in delta/theta activity with slight decreases in beta activity. The dominant alpha band is variably affected (272). Both atropine and scopolamine also depress the arousal response to photostimulation (273). In humans, atropine (1.2 mg, IV) inhibits the increased EEG activity produced by di-isopropyl fluorophosphate, a CHEI (274). These investigators also observed that atropine reduced abnormal discharges of the EEG in patients with grand mal epilepsy. Spontaneous and hyperventilation-induced petit mal EEG paroxysmal discharges can also be blocked with atropine (275). In animal studies, large doses of atropine and scopolamine have blocked seizures produced by exogenous acetylcholine and CHEIs (276), and also significantly decreased enflurane-induced EEG spiking activity (51). In clinically relevant doses, neither atropine nor scopolamine would be expected to have a significant therapeutic effect on seizure activity in humans.

Summary

Perioperative seizures have numerous potential etiologies. In general, when seizures occur during sur-

gery, their onset often coincides with the introduction of a specific anesthetic or analgesic drug. Conversely, postoperative seizures are more commonly due to nonanesthetic causes (277). However, there have been reports of postoperative convulsions that appeared to be caused by anesthetic or analgesic drugs administered intraoperatively via inhalation (30,34–36) or injection (e.g., intravenous [63,128], epidural [115], or peripheral nerve block [225]).

Some anesthetics appear to possess both proconvulsant and anticonvulsant properties (Table 1). One possible factor is an inherent pharmacodynamic variability in the responsiveness of inhibitory and excitatory target tissues in the CNS. This is well illustrated by the anticonvulsant and proconvulsant effects of progressively higher doses of local anesthetic drugs (64,229). This variability in neuronal responsiveness could also explain the conflicting findings for low versus high doses of fentanyl (136,142) and etomidate (175,178). Furthermore, biological variation in the individual patient's responsiveness to certain anesthetic drugs could be an additional contributory factor.

Differing structure-activity relationships might also explain why some anesthetic agents possess both proconvulsant and anticonvulsant properties. Relatively minor modifications in a drug's structure can influence its affinity for a specific receptor site and its intrinsic pharmacologic activity. For example, when methohexital was first introduced, convulsions were commonly encountered in patients with and without a history of epilepsy (278). Subsequent fractionation of the original compound into its two isomeric forms resulted in the identification of the isomer primarily responsible for this convulsive activity. In its present formulation (Brevital; Eli Lilly, Indianapolis, Ind.), the epileptogenic properties of methohexital are limited to patients with psychomotor epilepsy (11). However, compared with thiopental, excitatory effects are still more common with methohexital. The excitatory effects of methohexital are presumably due to its methylated structure (64). The inhaled anesthetic flurothyl (hexaflurodiethyl) ether and the intravenous anesthetic ketamine also illustrate how subtle changes in stereoisomerism can result in significant changes in structure-activity relationships (Figure 4). Flurothyl, a fluorinated ether analogue, reliably produces convulsions in nonepileptic patients, whereas its structural isomer isoindoklon has not been associated with seizure activity (279). Other examples of isomer or structural analogue relationships that produce differential effects on neuronal hyperexcitability include enflurane-isoflurane and meperidine-normeperidine.

In conclusion, the patient population (epileptic or

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nonepileptic), the method of documentation (EEG study or clinical observation), and the method of EEG analysis (cortical or depth electrodes) must be considered to properly analyze the proconvulsant and/or anticonvulsant properties of an anesthetic or analgesic drug. As more information regarding the site and mechanism of action of these drugs within the CNS becomes available with advances in in vivo imaging techniques (e.g., magnetic resonance imaging, positron emission tomography), our understanding of the conditions responsible for producing either proconvulsant or anticonvulsant properties should improve. Further advances in neurophysiology and neurochemistry will lead to improvements in the clinical use of anesthetic and analgesic drugs during the perioperative period.

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Clinical Reports

Continuous Spinal Anesthesia With Combined Hyperbaric and Isobaric Bupivacaine in a Patient With Scoliosis

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Key Words: ANESTHETIC TECHNIQUES, SPINAL—continuous.

We describe the anesthetic management of labor and cesarean delivery after failed epidural anesthesia using a continuous spinal technique with a combination of hyperbaric and isobaric local anesthetic solutions in a patient with severe kyphoscoliosis and congenital heart disease.

Case Report

A 31-yr-old gravida 1, para 0 woman with surgically repaired congenital heart lesions and severe kyphoscoliosis was scheduled for elective induction of labor at 39-wk gestation. She was born with a single ventricle and pulmonic valve stenosis and subsequently underwent multiple corrective procedures, including sequential bilateral Blalock-Taussig shunts and a modified Fontan procedure. The latter entailed placement of a valveless conduit from the right atrium to the pulmonary artery, tricuspid valve patch closure, and ligation of the earlier shunts. Effectively, the single ventricle became the left ventricle and the right atrium-pulmonary artery pressure gradient became the driving force for the pulmonary circulation. Cardiac catheterization 1 yr before admission demonstrated normal circulatory dynamics including normal right atrial pressure and pulmonary vascular resistance. She also had severe congenital thoracolumbar kyphoscoliosis for which she had never undergone corrective surgery (Figure 1).

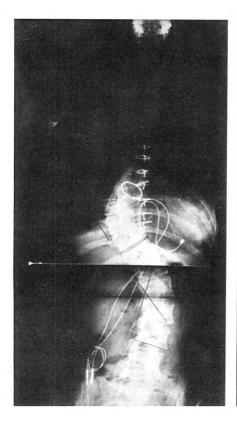
She had tolerated her pregnancy well and prenatal visits documented normal vital signs, finger pulse oxygen saturation, and fetal development. She complained only of mild exertional dyspnea during the last month of gestation. Monitors placed before induction of anesthesia for labor included an electrocardiogram, an automated blood pressure cuff on the leg, a finger pulse oximeter, and a right internal jugular central venous catheter.

A catheter was placed in the epidural space at L3-4 and advanced 2 cm, through which 8 mL of 0.5% bupivacaine was injected. Adequate anesthesia in T-10 to L-2 dermatomes was obtained, but in L2-5 dermatomes it was patchy and the sacral roots were not blocked despite an additional 6 mL of bupivacaine injected in the sitting position. Labor was induced with elective amniotomy and intravenous oxytocin. Although pain relief was adequate during early labor, the second stage would require sacral anesthesia and the ability to induce complete sensory block if forceps or cesarean delivery were required. Multiple attempts to improve the epidural anesthetic, such as changing the position of the catheter and of the patient, and the injection of 12 mL in 4-mL amounts of 2% lidocaine with epinephrine (pH adjusted) were unsuccessful and the epidural catheter was removed.

Continuous spinal anesthesia was chosen to replace the epidural anesthesia using a 17-gauge Weiss needle and a paramedian approach to enter the subarachnoid space at L2-3. An 18-gauge catheter was then advanced 2 cm into the subarachnoid space. Cerebrospinal fluid was freely aspirated and 0.75% hyperbaric bupivacaine with dextrose was injected in three 0.5-mL increments to a total of 1.5 mL (11.25

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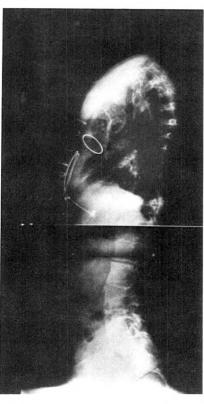


Figure 1. Posterior-anterior and lateral x-ray views of the chest and the lumbar spine.

mg) with the patient in the 60° head-up position and left uterine displacement. The initial level of pinprick anesthesia was T-4 on the left and T-10 on the right, which seemed to be related anatomically to the thoracic kyphosis. Despite two additional 0.3-mL doses of hyperbaric bupivacaine, the level of anesthesia remained unequal (the left sensory level increased to T-1 but the right remained at T-10). Again multiple positional maneuvers were utilized in an attempt to improve the extent of sensory block. Adequate surgical anesthesia was finally obtained with addition of 1 mL of 0.5% isobaric bupivacaine. Undiluted, preservative-free fentanyl, 10 µg, was then injected through the catheter.

Anesthesia was maintained at a T-4 level in the event that an emergency cesarean delivery was required. This was achieved with 1-mL injections of 0.75% hyperbaric bupivacaine followed by 1 mL of 0.5% isobaric bupivacaine every 2 h. An elective cesarean delivery for failure to progress and cephalopelvic disproportion was performed after 16 h of labor. The patient remained comfortable and hemodynamically stable throughout. A healthy, full-term male infant was delivered with Apgar scores at 1 and 5 min of 9 and 9.

Postoperative analgesia was provided with a single injection of 0.4 mg of preservative-free morphine through the spinal catheter. The catheter was left in place postoperatively for the first 12 h. Anesthesia completely resolved with no neurologic sequelae. The patient was monitored in the recovery room for 24 h with an apnea monitor and finger pulse oximeter. No respiratory depression occurred and she did not develop a postdural puncture headache.

Discussion

Epidural and spinal anesthesia in an obstetric patient with kyphoscoliosis may be difficult to achieve. Distortion of the spinal column and epidural space may prevent proper placement of an epidural catheter or uniform distribution of injected local anesthetic solution, resulting in an incomplete sensory block. If inadequate epidural anesthesia occurs, continuous spinal anesthesia may be employed, despite the increased incidence of postdural puncture headache (1). Elam (2) described the use of a subarachnoid catheter and hyperbaric lidocaine for labor and deliverv.

Hyperbaric local anesthetic solutions are commonly used for spinal anesthesia for cesarean delivery (3). In our patient, however, the normal distribution of a hyperbaric local anesthetic solution in the cerebrospinal fluid as determined by gravity was altered by severe lumbar scoliosis and relative straightening of the thoracic kyphosis. Specifically, the hyperbaric local anesthetic solution appeared to layer in the dependent areas of the spinal column, resulting in the unilateral block. The addition of isobaric bupivacaine in this situation improved the sensory block and raised the sensory level of anesthesia to T-4 bilaterally. The combination may have been effective merely due to the increase in total mass of local anesthetic. However, 0.5% isobaric bupivacaine is actually slightly hypobaric and may have "floated up" to produce the required anesthetic level (4).

Although development and trial of a 32-gauge spinal microcatheter is in progress at our institution, untested reliability and technical considerations mitigated against its use. Therefore, continuous spinal anesthesia was induced using a 17-gauge Weiss epidural needle and an 18-gauge catheter to assure free flow of cerebrospinal fluid. The possibility of development of spinal headache was discussed with the patient and considered an acceptable risk. The paramedian approach was used as it may be associated with a reduced incidence of headache (5).

The patient presented an unusual combination of anesthetic considerations with corrected congenital heart lesions and severe kyphoscoliosis in addition to the usual physiologic alterations of pregnancy. The anesthetic technique required flexibility in providing analgesia during labor and reliable induction of surgical anesthesia if necessary. The patient's cardiac status necessitated a titratable anesthetic technique to minimize sudden sympathetic denervation and the associated abrupt reduction in pulmonary artery pressure.

In conclusion, continuous spinal anesthesia may be an option in patients in whom regional anesthesia is desirable and in whom epidural anesthesia proves to be inadequate. In patients with severe kyphoscoliosis or otherwise altered spinal anatomy where continuous spinal anesthesia with hyperbaric local anesthetics has resulted in an inadequate or patchy block, the addition of isobaric local anesthetic may provide adequate anesthesia.

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Pharmacokinetics of Interpleural Lidocaine Administration in Trauma Patients

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Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interpleural. ANESTHETICS, LOCAL—lidocaine. PHARMACOKINETICS, LIDOCAINE—interpleural.

Local anesthetics have been administered interpleurally for postoperative pain relief (1), and the pharmacokinetics involved have been studied in spontaneously breathing postoperative patients (2,3). Local anesthetics also have been used interpleurally for pain relief in patients with multiple rib fractures (4). These patients may have abnormal pharmacokinetics because they have sustained chest trauma, but there are no data to support or refute this hypothesis. Similarly, patients with multiple rib fractures are usually mechanically ventilated, but the effect of mechanical ventilation on the lidocaine pharmacokinetics after interpleural injection is not known. The aim of this study was to provide information on the effect of chest trauma and mechanical ventilation on the pharmacokinetics of interpleural lidocaine.

Methods

Patients

After the approval of our protocol by our Human Investigation Committee, we studied 21 adult patients admitted to the intensive care unit with multiple injuries. Written informed consent was obtained from the patient or from his or her closest relative. The injury severity score was defined for each patient (5), and then he or she was assigned to one of three

groups of seven patients each. Group 1 consisted of patients with five or more unilateral rib fractures who required mechanical ventilation; group 2 consisted of patients with five or more unilateral rib fractures who did not require mechanical ventilation; and group 3 consisted of patients who were free of thoracic injury. The tidal volume used to ventilate group 1 patients ranged from 8 to 11 mL/kg, and the inspired oxygen fraction ranged from 0.3 to 0.5, i.e., it was sufficient to result in normal arterial oxygen tensions. Patients in groups 2 and 3 did not have respiratory failure and had normal blood gas tensions.

Interpleural Injection Procedure

A chest x-ray was performed in each patient in groups 1 and 2 before interpleural injection of lidocaine. If there was a hemothorax or pneumothorax, a chest tube was inserted. Then 1 mg/kg of 2% plain lidocaine diluted in 30 mL of normal saline was injected interpleurally over 2 min either through an interpleural catheter according to Reistad's method (1) or through the chest tube, if one was present. When the lidocaine was injected through the chest tube, the tube was clamped for 5 min and the patient was closely monitored by a physician for signs or symptoms of respiratory distress. In group 3, 1 mg/kg of 2% plain lidocaine was injected intravenously over 2 min.

Pharmacokinetic Study

Arterial blood samples were drawn in siliconized glass tubes at 0, 1, 3, 5, 10, 15, 20, 30, 40, 60, 90, 120, 180, 240, 300, and 360 min after the interpleural or intravenous injection of lidocaine; they were then immediately centrifuged at 4000 rpm for 10 min. The serum was then decanted and stored at -18° C until the time of the analysis. Lidocaine concentration was

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<u>Table 1</u>. Characteristics of Patients in the Three Groups

	Age (yr)	Weight (kg)	ISS
Group 1 (ventilated)	48 ± 12	74 ± 8	28 ± 7
Group 2 (not ventilated)	42 ± 21	66 ± 11	32 ± 5
Group 3 (intravenous)	27 ± 8	80 ± 10	29 ± 6

Values are mean ± sp. ISS, injury severity score.

measured using a model 3400 Varian gas chromatograph equipped with a nitrogen-specific detector and a 3 m \times 2 m ID column fitted with 3% OV 11 on 100/120 mesh Chromosorb W, AW, DMCS. Etidocaine was used as internal standard, and a single extraction in toluene was performed (6). In our laboratory, the limit of detection of lidocaine using this assay is 0.01 μ g/mL, and the coefficient of variation is less than 12% at 0.03 μ g/mL and less than 5% at 0.2 μ g/mL.

Noncompartmental analysis was used to fit the data. Terminal half-life ($T_{V2\beta}$) was calculated using log linear regression of the observed terminal curve, and the area under the curve (AUC) and the first moment of the AUC were calculated using the trapezoidal rule and extrapolated to infinity. The following parameters were derived for the three groups: the time to reach the peak (T_{max}) and, when present, the time to reach an early peak (T_{max}); the maximum peak concentration (C_{max}); the mean residence time (MRT); and the ratio of total body clearance (Cl) over bioavailability (f). Bioavailability was not directly determined, but Cl/f was derived from the formula Cl = f × D/AUC, where D is the dose injected.

Statistical Analysis

All values are expressed as mean \pm sp. Statistical differences among the group were sought using analysis of variance followed by the Kruskal–Wallis test. P < 0.05 was considered statistically significant.

Results

The three groups were not different with respect to age, weight, and injury severity score (Table 1). All seven group 1 patients had a chest tube, and four of seven group 2 patients had a chest tube.

Pharmacokinetic parameters are summarized in Table 2. C_{max} was significantly higher in group 1 than in group 2, and $T_{12\beta}$ was significantly longer in group 1 than in either group 2 or group 3. Total body clearance was significantly lower in group 1 than in

either group 2 or group 3. T_{max} was similar in groups 1 and 2. However, four group 1 patients had a biphasic elimination curve, whereas three had only a single peak. Among patients with a biphasic elimination curve, the early peak serum concentration was at 3 ± 2 min and the delayed peak was at 15 ± 5 min. For group 1 patients with a single peak, T_{max} was 17.5 \pm 15.5 min. The evolution of mean serum lidocaine concentrations for the three groups is shown in Figures 1–3. Examples of the different patterns of elimination from representative patients of group 1 (with biphasic elimination curve), group 2, and group 3 are shown in Figures 4–6.

Discussion

Our study shows that elimination of interpleurally administrated lidocaine was significantly delayed in mechanically ventilated trauma patients compared with elimination in patients breathing spontaneously. This difference was evident in the significant decrease in total body clearance associated with an increase in $T_{lk\beta}$. We did not find a significant difference in the pharmacokinetics of lidocaine after interpleural injection in spontaneously breathing patients with rib fractures (group 2) as compared with the pharmacokinetics after the intravenous injection (group 3) in trauma patients without rib fractures who were breathing spontaneously.

After interpleural lidocaine injection, absorption was rapid with T_{max} in the same range as that previously reported after interpleural administration of bupivacaine (2). However, considering the low dose injected in mechanically ventilated patients, the C_{max} was relatively high. In addition, we observed a biphasic absorption pattern in ventilated patients similar to that reported by Denson and colleagues after interpleural administration of bupivacaine (7). This is probably due to a flip-flop effect as previously described by Tucker and Mather (8) after epidural administration of local anesthetics. In addition, α_1 acid glycoprotein may be increased in trauma patients; however, we did not measure the protein binding because lidocaine has a "flow-limited" hepatic clearance, considered to be independent from protein binding.

In the present study, the bioavailability of lidocaine after interpleural administration is approximately 1. The clearance of lidocaine, which was lower in group 2 (interpleural injection in nonventilated patients) than in group 3 (intravenous injection), is in accordance with this. Furthermore, we observed a low clearance of lidocaine in group 1

Table 2. Pharmacokinetic Parameters in the Three Groups

	T1 _{max} (min)	T _{max} (min)	C _{max} (µg/mL)	T _{1/2 p} (min)	MRT (min)	CI/f (mL·min ⁻¹ ·kg ⁻¹)
Group 1 (ventilated)	3 ± 1 (n = 3)	17.5 ± 15.5 (n = 4)	2.09 ± 0.75*	151 ± 51°	207 ± 70	3.6 ± 1.34
Group 2 (not ventilated)	, ,	21 ± 13	1.03 ± 0.25	96 ± 23	147 ± 39	6.8 ± 1.9
Group 3 (intravenous)		-	<u></u>	92 ± 34	112 ± 37	8.7 ± 2.9

See text for definitions of abbreviations. In group 1, $T1_{max}$ is the time to reach an early peak for the three patients with a biphasic elimination curve. $^{4}P < 0.05$ versus groups 2 and 3.

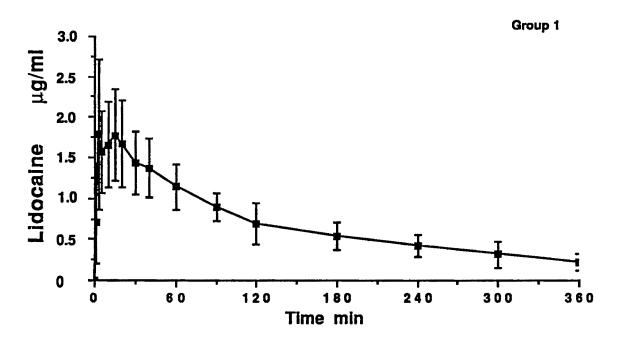


Figure 1. Serum lidocaine time-concentration curve in group 1 (interpleural injection in mechanically ventilated patients).

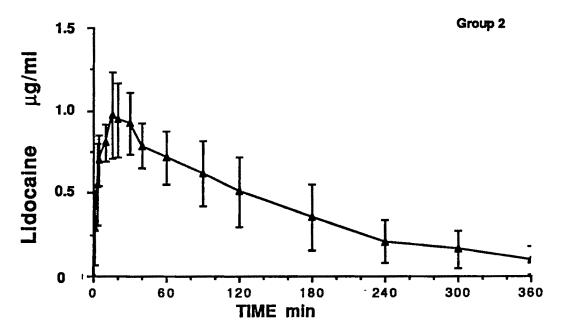


Figure 2. Serum lidocaine time-concentration curve in group 2 (interpleural injection in spontaneously breathing patients).

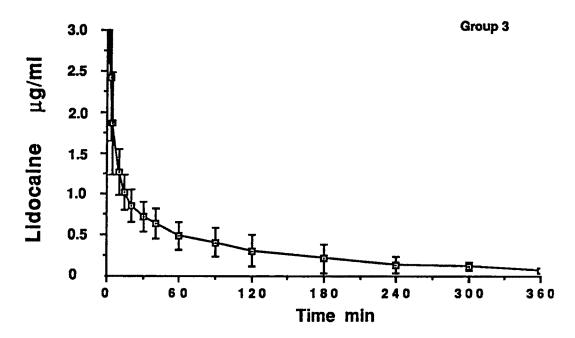


Figure 3. Serum lidocaine time-concentration curve in group 3 (intravenous injection).

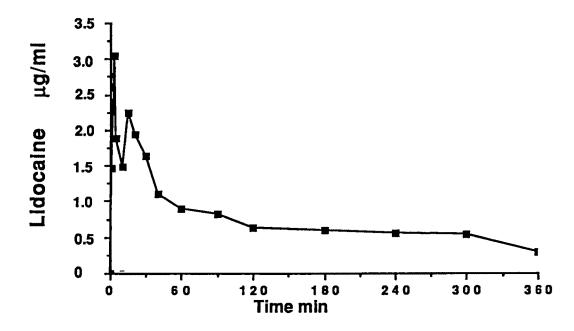


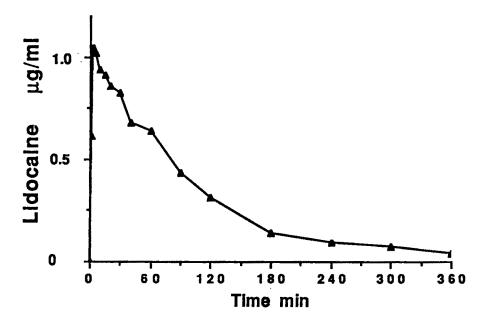
Figure 4. Elimination curve of serum lidocaine in a representative group 1 patient (biphasic elimination).

(interpleural injection in mechanically ventilated patients), and an area under the time-concentration curve (AUC) larger than the AUC in group 3. In any case, if the bioavailability was less than 1, the calculated clearance, which was already low, would be underestimated.

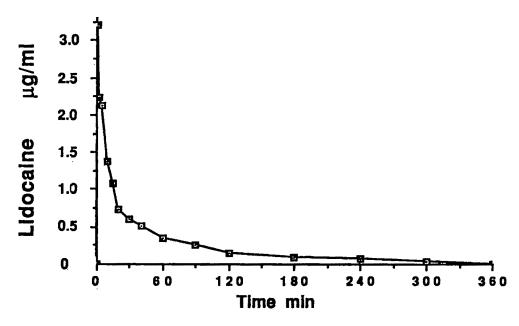
We observed the elimination $T_{\nu_2 \beta}$ of lidocaine to be longer in mechanically ventilated patients (151 \pm 51

min) than in spontaneously breathing patients (96 \pm 23 min)—both groups of patients with chest injuries. This latter value is in the same range as previously reported (9). The prolonged half-life may be due to reduced lidocaine clearance secondary to a decrease in hepatic blood flow (11), as previously described by Richard and colleagues (10). In fact, intermittent positive pressure ventilation causes a reduction in

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<u>Figure 5</u>. Elimination curve of serum lidocaine in a representative group 2 patient.



<u>Figure 6</u>. Elimination curve of serum lidocaine in a representative group 3 patient.

cardiac output with an associated decrease in hepatic blood flow (12).

From the clinical point of view, our data show the need for cautious administration of interpleural lidocaine in mechanically ventilated patients. Second, the clinical consequence of the low clearance of lidocaine—i.e., accumulation after multiple doses in mechanically ventilated patients—should be considered when interpleural injections are used to control pain.

In conclusion, although interpleural injection of local anesthetics has been found to be a useful method of obtaining analysis in thoracic trauma patients, the high peak serum concentrations of local anesthetics injected interpleurally (even when given in a low dose), the prolonged $T_{\mathcal{A}\mathcal{B}}$, and the biphasic elimination curves observed in ventilated patients suggest the need for further studies that specifically examine various agents and dosage regimens in these patients.

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Anesthetic Management of a Pregnant Patient With the Hyperimmunoglobulin E (Job's) Syndrome

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Key Words: GENETIC FACTORS, JOB'S SYNDROME. ANESTHETIC TECHNIQUES, EPIDURAL—immunologic deficiency. IMMUNE RESPONSE, DEFICIENCY—epidural anesthesia.

The hyperimmunoglobulin E (HIE) syndrome, also known as Job's syndrome, is a rare disorder associated with recurrent bacterial infections and abscesses of the skin and respiratory tract, primarily due to *Staphylococcus aureus*, and high serum immunoglobulin E (IgE) levels (1,2). The disorder begins in early childhood. There is no effective treatment, and these patients must present repeatedly for surgical drainage of abscesses. This case report describes the anesthetic management of a pregnant patient with HIE who presented for drainage of a hip abscess.

Case Report

A 21-yr-old gravida 2, para 1 black woman with a history of HIE syndrome presented to our hospital at 38 wk of pregnancy with a painful right hip. Her past medical history included recurrent *S. aureus* cutaneous and lung abscesses that required surgical drainage, as well as oral and vaginal candidiasis, dental abscesses, and active bronchitis. Of seven living siblings, one brother was affected by HIE; one sister with HIE had died of pneumonia. The patient's 1-yr-old daughter was thought to have the syndrome.

Aspiration of the hip joint yielded many white blood cells. The patient was afebrile, but two of four blood cultures grew coagulase-positive *S. aureus*. Laboratory findings included a hemoglobin of 7.4 g/dL and a white blood cell count of 8900. Pelvic examination revealed a closed cervix. She was treated with intravenous antibiotics (ceftriaxone and vancomycin).

Five days after admission, the patient was scheduled for surgical drainage of a suspected hip abscess. Premedication included oral metoclopramide and ranitidine to reduce gastric volume and increase pH. On arrival in the operating theater, the patient refused oral Bicitra. Monitoring included blood pressure cuff, precordial stethoscope, electrocardiogram, pulse oximeter, and capnograph. External uterine contraction and fetal heart rate monitors were placed by the patient's obstetrician, who remained in the operating room during the procedure. The patient was placed supine with left uterine displacement provided by placing a wedge under the right hip in order to prevent aortocaval compression. After preoxygenation with 100% oxygen, intravenous thiopental and succinylcholine were administered and cricoid pressure was applied until tracheal intubation was confirmed. Anesthesia was maintained with 50% nitrous oxide and 0.5%-1% isoflurane; muscle relaxation was provided with atracurium. The anesthetic was uneventful with stable hemodynamics and 100% oxygen saturation; uterine contractions were absent; the fetal heart rate declined during the anesthetic, from 150 to 120 beats/min. The patient was placed in the left lateral decubitus position for the procedure; incision of the joint capsule yielded pus, but no bacteria were reported on Gram stain. The joint was irrigated and closed with drains in place. At the end of the procedure, infrequent uterine contractions were observed. Several brief episodes of fetal heart rate deceleration were observed during emergence, which was prolonged and marked by coughing, production of copious yellow sputum, and brief periods of desaturation. After the patient was extubated, fetal heart rate returned to a normal range. Irregular uterine contractions subsided within 1 h. Monitoring continued in the labor suite for 6 h postoperatively.

The remainder of the surgical course was uneventful, with rapid resolution of pain and rapid return to ambulation. No organisms were found on culture of the joint fluid. The patient remained hospitalized,

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and, 2 wk later, a normal-appearing 2950-g female infant was delivered vaginally, at term, with Apgar scores of 8 and 9 at 1 and 5 min. Anesthetic management for the delivery consisted of analgesics given parenterally during labor and delivery. The postpartum course was uneventful, and the patient was discharged 4 wk after her admission. Three months later a large abscess in the right thigh was drained; the operative course was complicated by a lingular pneumonia. Seven months later a large temporal subcutaneous abscess was drained. Ten months later a large loculated empyema required thoracotomy for open drainage.

Discussion

The HIE syndrome was first described in two children with recurrent large staphylococcal abscesses without local inflammation (1). In addition to cutaneous abscesses, the disorder has been reported in association with bronchitis, pneumonia, empyema, osteomyelitis, sinusitis, otitis media and externa, mastoiditis, sialitis, gingivitis and tooth abscesses, lymphadenitis, urinary tract infections, giardiasis, axillary and perirectal abscesses, keratoconjunctivitis, and mucocutaneous candidiasis (oropharynx, lungs, ear, gastrointestinal tract, vagina) (2-6). The abscesses are frequently large when first detected. Bacteremia and other deep infections (visceral, renal, cardiac, or central nervous system abscesses) are unusual in reported series. The infectious organism is primarily S. aureus, but Hemophilus influenza pneumonia has been reported.

The primary immune defect in HIE is unknown; however, total immunoglobulin is normal, with increased IgG, markedly increased IgE, and decreased IgA and IgM. Antistaphylococcus IgA is markedly decreased in HIE, but IgA specific to gram-negative organisms and streptococcus may be normal. The rate of infection in HIE is inversely correlated with IgA levels (4). A local defect of bacterial killing was originally proposed (1); defective chemotaxis but normal killing of opsonized *S. aureus* is reported, but this is variable (2) and less than that observed in patients with other, better-defined disorders of chemotaxis. Mononuclear cells in HIE produce an inhibitor of chemotaxis when exposed to S. aureus in vitro, but the clinical significance of this phenomenon is unknown. Delayed hypersensitivity reactions may be abnormal, and specific T-lymphocyte subpopulation deficiencies have been reported (6).

There is no effective therapy for the prevention of recurrent infections. For acute abscesses, recom-

mended therapy is local care, early surgical drainage, and intravenous antibiotics appropriate to staphylococcus or hemophilus. The frequency and severity of abscesses may be reduced by prophylactic oral antibiotics, such as dicloxacillin. Trimethoprim-sulfamethoxazole has been an effective substitute for prophylaxis in patients who develop mucocutaneous candidiasis. Intravenous γ -globulin may be an effective treatment. Plasmapheresis has been successful for severe complications and failure of antibiotics (6).

This patient displayed many of the features of HIE. At the time of presentation, she had an active, presumably *S. aureus* bronchitis and skin scarring from chronic infection, and was thought to have *S. aureus* bacteremia. The anesthetic management for this case was complicated by the patient's near-term pregnancy. Epidural anesthesia is favored by practicing anesthesiologists and obstetricians for management of labor pain, delivery, and cesarean sections because these are safer for the patient and infant. One risk of epidural or spinal anesthesia is that of producing an epidural abscess.

The incidence of epidural abscess reported in the general medical literature is very low; the predominant organism is *S. aureus*; the bacteria are usually transmitted by the blood to normal epidural tissue from a distant site (7). The incidence of infection directly related to epidural and subarachnoid puncture is also low, with few case reports (8–11). Infection related to chronic epidural catheter placement has been reported, but does not have the same significance as spontaneous infection (12). The rule of practice is to avoid placing a needle through or near "infected skin" such as cellulitis, abscesses, or decubitus ulcers (13).

In the patient with HIE, however, this rarity of epidural infection may not apply. Several factors may increase the risk of spinal epidural abscess formation in patients with HIE. Epidural needle puncture through skin chronically infected with S. aureus can carry an inoculum to the epidural space. Nearby or distant abscesses may seed spontaneously, or when incidental epidural vein puncture occurs, allowing bacterial entry from the bloodstream. Staphylococcus aureus, most frequently associated with epidural abscesses, are the bacteria responsible for the abscesses of HIE and are likely to be drug-resistant due to chronic antibiotic prophylaxis. In addition, the immune system of the HIE patient is compromised. Successful management of epidural abscesses includes rapid diagnosis and surgical drainage. In HIE, the abscess may not produce local inflammation or spinal pain until late in the clinical course, thus

delaying diagnosis until neurological signs are established.

This case is presented to increase awareness of this condition and to stimulate reporting of case data on other HIE patients. In the future, the natural history of the disease will change with improved therapy, but the incidence of cases will also increase as these individuals reach adulthood and reproductive status with greater frequency.

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Extremity Tourniquet Deflation Increases End-Tidal Pco₂

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Key Words: EQUIPMENT, TOURNIQUET—effects of deflation.

Since the advent of capnography, anesthesiologists have been better able to measure and detect acute perioperative variations in end-tidal partial pressure of carbon dioxide (ET Pco₂). We have recently observed an acute increase in ET Pco₂ after the release of an extremity tourniquet during orthopedic surgery. A sudden increase in Pco₂ may have detrimental effects in certain patients, such as head-injured patients with an elevated intracranial pressure. These patients frequently undergo orthopedic and other procedures on the extremities with an arterial tourniquet in place. The purpose of the present study was to investigate the effect of tourniquet release on ET Pco₂ measurements in patients undergoing extremity surgery requiring use of a tourniquet.

Methods

Twenty-four patients undergoing extremity surgery requiring arterial tourniquets were included at random in this study without regard to ASA physical status; they were divided into two groups. Group A consisted of 12 patients with upper extremity surgery, and group B consisted of 12 patients undergoing lower extremity surgery. All patients received general tracheal anesthesia. Anesthesia was induced with thiopental (4–5 mg/kg, intravenous) and tracheal intubation was facilitated by succinylcholine (1.5 mg/kg, intravenous). Anesthesia was maintained with either isoflurane or halothane plus nitrous oxide in oxygen. Patient monitoring systems included an electrocardiogram, a blood pressure sphygmomanome-

ter, pulse oximetry, esophageal temperature, and end-tidal gas analysis by mass spectrometry (SARA-cap AMIT). The lungs of all patients were ventilated mechanically, and ET Pco₂ was maintained at approximately 30 mm Hg. End-tidal Pco₂ values were recorded immediately before tourniquet deflation and 1, 2, 3, 4, and 5 min after tourniquet deflation. Data were analyzed for statistical significance for within and between groups using multifactor analysis of variance. Linear regression analysis and correlation coefficients were calculated for the tourniquet time and peak increase in ET Pco₂. A P value less than 0.05 was considered to be statistically significant.

Results

Table 1 shows the mean ET Pco₂ values of both groups. The increase in ET Pco2 ranged from 1 to 12 mm Hg after the release of the upper extremity tourniquet and from 5 to 18 mm Hg after the release of the lower extremity tourniquet. The increase in ET Pco₂ was statistically significant at all time intervals after releasing both upper and lower extremity tourniquets when compared with ET Pco₂ values before the tourniquet was released (P < 0.05). A more significant increase in ET Pco2 was noted after the release of the tourniquet in patients with lower extremity surgery when compared with the increase in Pco_2 in patients with upper extremity surgery (P <0.05). The peak increase in ET Pco₂ was threefold higher in patients with surgery involving lower extremity when compared with upper extremity after the release of arterial tourniquets. There was no correlation between the duration of tourniquet time and increase in ET Pco2. The tourniquet time varied from 42 to 90 min.

Discussion

Arterial Pco₂ is a major factor influencing cerebral blood flow and intracranial pressure (1,2). Not infre-

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<u>Table 1</u>. End-Tidal Pco₂ Values Immediately Before Tourniquet Release and 1–5 min After Tourniquet Release in Patients Undergoing Upper- and Lower-Extremity Surgery

	ET Pco_2 , mm Hg (mean \pm sem)			
Time	Upper-extremity*	Lower-extremity		
BTR	29.7 ± 1.3	31.7 ± 1.1		
1 min ATR ^b	31.6 ± 1.5	37.8 ± 0.9		
2 min ATR ^b	32.5 ± 1.6	40.1 ± 1.0		
3 min ATRb	32.2 ± 1.7	40.5 ± 1.1		
4 min ATR ^b	31.8 ± 1.6	39.6 ± 1.0		
5 min ATR ^b	32.1 ± 1.6	38.3 ± 1.0		

ATR, after tourniquet release; BTR, immediately before tourniquet release; ET Pco_2 , end-tidal partial pressure of carbon dioxide.

*ATR increases in Pco₂ in lower-extremity group are significantly greater than increases in upper-extremity group (P < 0.05, multifactor analysis of variance).

Esignificantly different when compared to BTR (P < 0.05, multifactor analysis of variance).

quently, patients with increased intracranial pressure present to the operating room for extremity surgery. To our knowledge, this is the first study to use capnography to demonstrate a significant elevation of ET Pco₂ after the release of an extremity tourniquet. Typically, this elevation of ET Pco₂ reflects elevated Paco₂, which can further acutely increase intracranial pressure.

We have not investigated the mechanisms responsible for an increase in Pco₂ after the release of a tourniquet in our patients. Possible mechanisms include (a) accumulation of acid metabolites during the ischemic period of tourniquet inflation, which, upon reperfusion of the extremity, are buffered by plasma bicarbonate with a concomitant acute increase in arterial Pco₂ (3); and (b) production by anaerobic metabolites of a temporary state of reactive hyperemia and a hypermetabolic state upon recirculation.

Other authors have previously reported the metabolic changes due to tourniquet-induced ischemia. Benzon et al. found increased venous lactic acid levels that persisted for 10 min after tourniquet deflation (4). Haljamae and Enger found a 225%–300% increase in lactate content of skeletal muscle during tourniquet use, with return to baseline levels 5 min after tourniquet deflation (3).

More recently, Goto et al. studied the effects in dogs of intravenous methylprednisolone injection into one hindleg and placebo injection into the opposite hindleg on tourniquet ischemia. They reported that hindleg venous oxygen tension and pH decreased, and Pco₂, lactic acid, creatine kinase, and lactic dehydrogenase rose steadily 30, 60, and 120 min after tourniquet inflation in both legs (5). However, these changes were significantly less in the methylprednisolone-treated legs.

Our data indicate that a more significant increase in Pco₂ occurred when a lower extremity tourniquet was used. This is perhaps not unexpected in view of the greater skeletal mass of a lower as compared with an upper extremity. We found no correlation between the duration of tourniquet inflation time and the increase in ET Pco₂. However, the tourniquet was inflated for more than 1 h in all but one case (42 min).

In conclusion, our study demonstrates that there is a significant increase in ET Pco₂ levels after the release of an extremity tourniquet. This increase is threefold higher in patients with surgery involving the lower extremity when compared with those with surgery in the upper extremity. We recommend monitoring of ET Pco₂ and initiation of hyperventilation just before and for a few minutes after a tourniquet is released to maintain the desired level of Pco₂, especially in patients with increased intracranial pressure.

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Letters to the Editor

Ampullary Hypertrophy: Malignant or Benign?

Key Words: EQUIPMENT, AMPULES—narcotics. ANALGESICS, NARCOTICS—ampule contents.

To the Editor:

It was with interest that I read the letter from Kennedy and colleagues (1) concerning overfill in fentanyl and sufentanil ampules. The overfill issue is addressed in The United States Pharmacopeia (USP). The USP (2) lists recommended standards (Table 1)¹ for the amount of overfill allowable in containers for injectable drugs (i.e., ampule, vial). Overfill is permitted in the containers to allow the withdrawal of the labeled volume of medication. Although the amount of overfill recorded by Kennedy et al. exceeds the USP recommended standards (Table 1), a problem still exists even if these standards are met. For example, 15 fentanyl 10–mL ampules (an amount commonly used in major heart procedures) yields an additional 7.5 mL of fentanyl using the allowable USP standards.

This problem affects not only anesthesiology personnel but also the many pharmacists practicing in the operating room today. In institutions with an operating room pharmacy satellite, the operating room pharmacist is responsible for dispensing controlled substances and maintaining accurate records concerning the use and disposition of these medications. On several occasions anesthesiologists at my institution have been questioned because they had recorded on their anesthesia records a greater quantity of

<u>Table 1</u>. United States Pharmacopeia Recommended Standards for Amount of Overfill

Ampule size (mL)	Amount of overfill (mL)
0.5	0.1
1.0	0.1
2.0	0.15
5.0	0.3
10.0	0.5
20.0	0.6
30.0	0.8
≥50.0	2% of volume

fentanyl than was dispensed for use; it was discovered that the additional fentanyl utilized could be attributed to overfill

There are no easy solutions to this problem. The most practical solution may be for the anesthesiologist to discard the overfill after withdrawing the contents of the ampule into a syringe. The excess drug can be expelled into a "sharps" container. By so doing, the anesthesiologist will start the case with an amount of controlled substance equal to that stated on the ampule's label. Diversion of the drug overfill contained in the ampule for illicit purposes is still possible with this remedy as the excess narcotic can just as easily be injected into a sterile vial. However, drug diversion can be lessened significantly if a controlled substance tracking system is used in which narcotics are dispensed on a per case basis. With this type of a system, narcotics are dispensed by the pharmacist to the anesthesiologist for one case at a time. Narcotics for the next case can only be obtained by returning the previous case's unused controlled substances. Hence, instead of the anesthesiologist receiving a standard quantity of controlled substances for the day irregardless of his or her case load, a quantity of drug sufficient for the case in question is received. If, for example, 2 mL of fentanyl is required for the case, the amount of overfill available would be 0.1 mL. This is in contrast to a system where, for example, the anesthesiologist is given four 5-mL ampules of fentanyl at the beginning of the day for his or her cases. In this instance, 1.2 mL (0.3 mL \times 4) of fentanyl overfill would be available. These examples illustrate how a per case narcotic system can greatly reduce the amount of narcotic overfill available at any point in time.

Modification of the ampule's volume to be more representative of the labeled drug quantity may, however, be the ultimate solution to this problem. Care must be taken by the manufacturer not to decrease the ampule drug volume to such an extent that the labeled quantity of drug cannot be withdrawn. The manufacturing processes used by various drug companies may place constraints on their ability to modify the volume of drug contained in an ampule in the near future.

In any event, overfilling of ampules, especially those containing narcotics, represents an issue that must be addressed. It would be prudent for the Department of Anesthesiology and the Pharmacy Department in each institution to work together to develop a policy that would be best for their particular institution.

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To the Editor:

In a recent letter to the editor, Kennedy et al. (1) state that the small amount of fentanyl and sufentanil in ampules that exceeds the labeled amount is a matter of danger and concern. The extra narcotic, photographically illustrated in their letter, is indicted as a potential source of overdose in patients, imprecision in record keeping, and drug abuse in practitioners. We wish to point out several flaws in this argument and in the interpretation of the photograph used to support it.

As Kennedy et al. state, it is the apparent standard of pharmaceutical manufacturers to place slightly more volume in a single-dose ampule than is actually indicated on the label; the purpose appears to be to allow the practitioner some leeway in filling his or her syringe from the ampule, so that the patient receiving "one ampule" of a drug would not be cheated of the full amount when a few drops are left adhering to the walls of the ampule, or trapped in the detached cap. We would all agree that the responsibility for accurate dosing of such powerful drugs such as fentanyl and sufentanil rests with, and must always rest with, the practitioner.

Although the full amounts in the ampules are indeed somewhat greater than the labels state, the discrepancy is far less than suggested by Kennedy et al. Their photograph illustrates a 10-mL syringe containing the contents of a 5-mL ampule. With the syringe held vertically and the plunger at the 10-mL mark, the fluid level is seen at the 4.2-mL mark. They erroneously conclude that this represents a 5.8-mL volume. They do not take into account the fact that syringes with bevelled barrels, like those depicted, have bevelled gaskets at the end of their plungers in order to make up for the "excess" volume at the mouth created by the bevel. This volume is calculable as the volume of a cone, V = 2rh/3, with r being the inner radius of the barrel and h the height of the bevel. In addition, evacuation of such a syringe in the normal fashion is necessarily incomplete, with fluid left behind in its tip and the attached needle. This can be easily demonstrated by aspirating air into a syringe prefilled with fluid to the 5-mL mark. When the plunger is pulled back to the 10-mL mark, the base of the meniscus will be at 4.6 mL. This represents a significant portion of the purported discrepancy cited by Kennedy et al.

As for the potential for drug abuse, each ampule in its entirety is a potential source of narcotics for the abuser, and there seems to us to be nothing special about the less than 10% additional drug solution that the manufacturers add as a courtesy. Any practitioner can "shave" small (or large) amounts from recorded dosages for private use, and there is no shortage of anecdotal evidence that this is in fact done, often with consequences more tragic for the practitioner than for the patient. Significant amounts of narcotics, frequently entire ampules, are "wasted" at the end of each case, and this can be easily exploited by the drug user in the furtherance of his or her habit. The residual amount of narcotic in the ampule that exceeds the labeled amount pales in comparison.

In actual practice, one draws up an estimated volume from an ampule, evacuates the air from the syringe, and presses the liquid to the end of the syringe. Only then do the volumetric markings on the syringe have their true meaning. The small excess volume is discarded, whether because it has adhered to the walls of the ampule, been left in the discarded syringe, been "wasted" at the end of the case, or has simply fallen victim to the omnipresent forces of entropy. We believe that the excess amount in a singledose ampule, be it sterile water or sufentanil, is the pharmaceutical company's way of "giving good weight" by giving slightly more than is required by the user, a practice as old and as time-honored as the baker's dozen. Practitioners uniformly recognize and make allowances for this practice, and its clinical or social significance seems negligible.

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Another Complication of Tracheal Intubation

Key Words: EQUIPMENT, TUBES—endotracheal. INTUBATION, TRACHEAL—complication.

To the Editor:

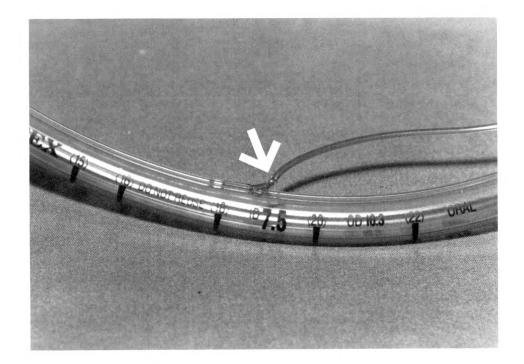
We wish to call attention to an unusual complication that emphasizes the fact that despite appropriate preanesthetic checks designed to minimize mishaps, these can still occur.

After preoxygenation, induction of general anesthesia was accomplished in a 27-yr-old woman scheduled for

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 $\underline{\text{Figure 1}}$. Observe the kink of the pilot balloon line at its junction with the ETT.

laparoscopy using thiamylal and, following succinylcholine, the trachea was intubated using a No. 7.5 Portex endotracheal tube (ETT). The ETT cuff was then inflated with 5 mL of air.

At this time, pressure in the pilot balloon was appropriate, breath sounds were present and equal bilaterally, and tracheal intubation was confirmed by capnography. Despite what appeared to be satisfactory inflation of the pilot balloon, an air leak soon became apparent at an inspiratory pressure of 20 cm H₂O (tidal volume of 600 mL and a respiratory rate of 12 breaths/min). With injection of more air, the pilot balloon became noticeably overinflated, and the leak persisted. Direct laryngoscopy revealed correct tracheal placement of the tube with no evidence of the cuff overriding the vocal cords.

Subsequently, as the tube was being replaced, it became evident that the pilot balloon line (the tube that links the pilot balloon with the ETT cuff and permits its inflation) had kinked at its junction with the ETT (Figure 1), thus allowing pressurization of the pilot balloon without inflation of the cuff.

A review of the literature revealed a published case describing occlusion of the pilot balloon line (1) and a subsequent inability to deflate the ETT cuff before extubation. Our letter is apparently the first report, however, of the inability to inflate the cuff of an ETT secondary to obstruction of the line that binds the pilot balloon with the ETT cuff

This experience reiterates that in addition to an adequate check of the endotracheal tube before induction of anesthe-

sia, care must be taken to prevent occlusion of the pilot balloon line after ETT insertion. Modification of the design of oral ETTs—moving the junction of the pilot balloon line with the outer surface of the ETT itself upward to a location nearer the ETT connector—might be beneficial.

With such a modification, the junction would no longer be hidden in the oral cavity and thus would at all times be more readily accessible for inspection.

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Treatment of Nesacaine-MPF-Induced Back Pain With Calcium Chloride

Key Words: ANESTHETICS, LOCAL—2-chloroprocaine.

To the Editor:

Recently, Fibuch and Opper (1) reported eight cases of back pain after the epidural injection of Nesacaine-MPF. The back pain occurred after the anesthesia had receded and was not relieved with narcotics. Because episodes such as this had not occurred with other local anesthetics, including Nesacaine-CE, the authors concluded that the disodium ethylenediaminetetraacetic acid (EDTA) was causing local binding of calcium. It was hypothesized that the localized binding of calcium had created tetany from hypocalcemia in the paravertebral musculature. A recent case at our institution indicates that hypocalcemia may indeed be related to this type of back pain.

A healthy 30-yr-old woman requested an epidural anesthetic for removal of a vaginal cyst. The patient was premedicated with 2 mg of intravenous midazolam. After local infiltration with 1% lidocaine, a test dose of 1.5% lidocaine with 1:200,000 epinephrine (3 mL) was injected epidurally at L3-4 without adverse effect followed by Nesacaine-MPF (23 mL) to provide anesthesia for the procedure.

After the sensory blockade had regressed, the patient began to complain of severe back pain (75 min after the last injection of Nesacaine). The pain was so intense that the patient was unable to get into a comfortable position either lying or sitting. The pain was primarily in the lumbar region, but also involved the thoracic region to some extent. She was then given 550 mg of oral naproxen but had no relief 2 h later. Because of the severity of the pain and the possibility that disodium EDTA might be the causative agent, the patient was given calcium chloride (1 g) by slow intravenous infusion (over 5 min). After approximately 300 mg of the calcium chloride had been given (2 min after injection was started), the patient stated that she felt much better, and she was able to sit comfortably in the chair. The patient was discharged 15 min later with such improvement that there was only some residual pain localized to the point of injection.

Reports of severe back pain have surfaced recently after the epidural use of Nesacaine-MPF. The cause of the back pain is unknown, but Fibuch and Opper surmise that it is due to the disodium EDTA added as a preservative. Ethylenediaminetetraacetic acid is well known to bind calcium and is used to treat severe hypercalcemia. Localized absorption of EDTA from the epidural space might create a state of hypocalcemia leading to tetany of the paravertebral musculature. The fact that this patient had such a dramatic improvement after the calcium chloride was infused indicates that hypocalcemia may be related to the back pain associated with Nesacaine-MPF.

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Reference

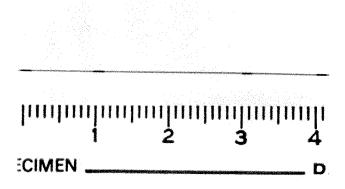
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Vanishing Calibration Marks on a Spinal Catheter

Key Words: EQUIPMENT, CATHETERS—spinal. ANESTHETIC TECHNIQUES, SPINAL—continuous.

To the Editor:

To reduce the incidence of pos'dural puncture headache after continuous spinal anesthesia 32-gauge (TFX Medical) and 28-gauge (Kendall) intraspinal catheters have been developed. Both catheters have centimeter markings to allow proper depth insertion. We would like to report two



<u>Figure 1</u>. Photographic enlargement of a 32-gauge catheter (*top*) showing markings at 1-cm intervals. Note the absence of the mark at the 2-cm level on the catheter. The mark was washed away by cerebrospinal fluid.

cases in which small amounts of fluid (cerebrospinal fluid or local anesthetic) "washed off" the centimeter markings during attempts to insert intraspinal catheters. This can make positioning of the catheter difficult.

In the first case, fluid on the anesthesiologist's glove washed off the markings on a 32-gauge catheter during the insertion procedure (see Figure 1). In the second case, a 28-gauge catheter was used for a differential spinal in a patient with chronic back pain. The catheter was removed after 3 h at the end of the procedure. When the catheter was removed several of the centimeter markings had washed off the catheter. The only way to determine that a catheter fragment had not been left in the patient was to measure the total catheter length.

As the material used for the centimeter markings can be easily dislodged, is there a risk of deposition of foreign material in the subarachnoid space? Additional study will be required to determine the clinical significance of this observation.

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Cost of Invasive Monitoring: A Yet Unresolved Issue

Key Words: ANESTHESIA, CARDIOVASCULAR—costs. MONITORING, costs. ECONOMICS, costs of monitoring.

To the Editor:

We read the interesting recent comparison by Pearson et al. (1), which reported on the cost/benefit ratios of using central venous pressure (CVP) and pulmonary artery (PA) monitoring in cardiac surgical patients. They studied 226 adults undergoing elective cardiac operations. Patients were divided into five different groups, according to the type of catheter used for monitoring. Patients monitored with CVP catheters, PA catheters, or mixed venous oxygen (Svo₂) measuring PA catheters were assigned to groups I, II, and III, respectively. Some patients from group I (CVP group) were reassigned to receive either a conventional PA catheter or Svo₂-measuring PA catheter into groups IV and V, respectively. The authors concluded that patients with good cardiac function could safely undergo cardiac surgery with monitoring of only CVP and left atrial (LA) pressure at considerably reduced cost.

We have several problems with this report:

- (a) Table 1 of the report reveals that 74 patients were initially assigned to group I (CVP group). Forty-six of these 74 patients were subsequently "rerandomized" to different groups (IV and V) to receive PA catheters. This reassignment from group I to groups IV and V should have been dealt with differently, by a crossover study design.
- (b) Authors cited "ethical considerations" for justifying rerandomization, but these ethical considerations are not well defined. We presume that poor left ventricular ejection fraction was the main reason for rerandomization of patients from group I to groups IV or V. If this is the case, we would like to point out that the difference in the mean left ventricular ejection fraction values between groups I and V is not statistically significantly different enough (64% ± 9% vs 58% ± 13%) to justify this rerandomization.
- (c) Of a total of 226 patients, only 28 patients were managed with CVP only, and the remaining 198 patients received PA catheters (conventional or Svo₂-measur-

- ing). As the mortality from coronary artery bypass surgery in most centers is less than 2% (2), a substantially larger number of patients is required in group I (CVP group) to make evaluation of safety valid.
- (d) The authors mention that all the patients had LA catheters placed after sternotomy and that this catheter was used in the early postoperative period. When an LA catheter was used, comparisons between outcomes with CVP and PA catheter alone become meaningless. Cost should have been compared as the cost of CVP plus LA catheter in group I versus the cost of PA catheter only in the remaining groups. Did the surgeons charge for the placement of the LA catheter? If not, they were obviously being charitable. If they did charge, this is a cost to the patient that should be included in the analysis. Also, charges for the transducer system used for an LA catheter constitute additional cost to the patient.
- (e) We cannot find a justification for placing LA catheters in patients who already have PA catheters in place for monitoring. Left atrial catheter placement is not innocuous and is associated with embolic and hemorrhagic complications (3). One cannot make inferences as to the "safety" of CVP plus LA catheters based on mortality data alone. Morbidity data are necessary in view of the potential for bleeding and systemic air embolism associated with LA catheters.

The authors' attempt at addressing the very important issue of the cost of invasive monitoring would have been very valuable if more patients had been included in group I (CVP only) and if the authors had included the "hidden" cost of LA catheters when comparing costs between CVP and PA catheters (remaining groups). The important issue of the cost of invasive monitoring remains unresolved.

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In Response:

Thank you for allowing us the opportunity to reply to the letter of Shah et al. We would like to respond to each of their concerns.

Shah and associates state that, "Reassignment from group I (CVP monitor) to groups IV (standard PA catheter)

and V (Svo₂-measuring PA catheter) should have been dealt with differently, by a crossover study design." A crossover design assigns a patient to receive one therapy for a period of time, then has him or her "cross over" to receive a second therapy for another period of time (1). This type of study design cannot be carried out if a patient will only receive one exposure to the experimental therapy—in this case, monitoring for the surgical procedure. Shah et al. do not appear to understand the term "crossover design," or perhaps we don't.

Shah et al. appear not to have understood how our reassignments from group I to groups IV or V were carried out. As stated in the methods and materials section, the decision to rerandomize was made by the attending anesthesiologist. As stated in the discussion section, no attempt was made to influence the attending anesthesiologist's decision, as we continue to believe that the frequency of these decisions was itself important outcome data. As also mentioned in the discussion section, published recommendations were used in the decisions to use PA catheters. Indications for PA catheterization as cited in references included, but were not limited to, poor left ventricular ejection fraction, recent myocardial infarction, left main coronary artery disease, cardiac valvular disease, and combined coronary-valvular disease. In light of these multiple indications, it is not surprising that patients in group V had similar ejection fractions, compared with our patients in group I.

We agree that 29 patients are not adequate to completely evaluate mortality in a procedure with a relatively low mortality rate. The focus of our study, however, was the cost of various monitoring technologies. We clearly demonstrated that use of a CVP catheter was associated with a savings to the patient of more than \$250, compared with the conventional PA catheter, and more than \$530 per patient compared with the Svo₂-monitoring catheter.

Dr. Shah was concerned about the cost of LA monitoring. As we mentioned in the methods section, all patients had LA catheters inserted. Because costs associated with this catheter were present in all groups, it was unnecessary to analyze separately the costs of the LA catheters and transducer systems.

Although potential risks do exist with placement of LA monitors, no patient in our study had mortality or morbidity associated with their use. We remind Dr. Shah and colleagues that use of PA catheters is itself associated with considerable risk. Dr. Rao's own study reported one death, and a 5% incidence of major complications, including ventricular perforation, PA perforation, and pulmonary infarction (2). In fact, our zero mortality and/or morbidity associated with LA monitors compares very favorably against the above data from PA catheters.

The criticisms of Shah et al. do not alter our results or convince us to alter our analyses of them. We demonstrated that selected patients could safely undergo cardiac surgery with CVP and LA monitoring; further, that use of Svo₂ monitoring added significant cost to patient care without discernible change in patient outcome.

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Bupivacaine-Induced Cardiac Arrest

Key Words: ANESTHETICS, LOCAL—bupivacaine. TOXICITY, BUPIVACAINE.

To the Editor:

After reading the report by Long et al. of the successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary bypass (1), one is left wondering about some unanswered questions relative to such issues as selection of patient, of anesthesia, and of a proper patient/ anesthesia match.

One should readily concede that the resourcefulness, persistence and, if you wish, "generalship" displayed by all involved are remarkable and should be commended.

On the other hand, was conduction anesthesia really appropriate for this patient? A young woman, at work, suffers a mutilating and disabling injury; under ordinary conditions such a person would be besieged, if not overwhelmed by a multitude of reactions: anger (why me? I was only doing my work!); anxiety (what about my children? what about my hand? will I be able to work again?); fears for loss of physical integrity (will I be attractive enough without . . . ?); deprecation (if I had not looked that way or the other way then this would not have happened). Why should such a person be forced to lie still and awake for many hours while strangers work on her hand? (We may call it operating, but to such a person hacking may sound and feel more appropriate.) Would it not be more appropriate to provide a few hours of blissful unawareness? If a full stomach were an issue then cricoid pressure could have been applied and, in any case, 5.5 h had elapsed since food ingestion.

Why repeat a block while the operation is in progress, and, further, why the switch to bupivacaine? Lidocaine had been effective: why the switch? The dangers attendant to unintentional intravascular injection of bupivacaine are well known. Cardiac arrests occurring at the time of presumed epidural injection of bupivacaine have been reported. If bupivacaine can find its way into the vascular stream from a relatively avascular space such as the epidural space, wouldn't there be an even greater danger that it could find its way into the vascular stream from the axillary space, which is so rich in arteries, veins, and lymphatics?

One is left with the uneasy suspicion that this cardiac arrest was quite preventable. One is also left with considerable reservations about the validity of a policy that all injuries to the hand should be managed with regional anesthesia.

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Transient Large Upright T-Waves During Electroconvulsive Therapy

Key Words: ANESTHESIA, ELECTROCONVULSIVE THERAPY.

To the Editor:

Khoury and Benedetti (1) reported T-wave changes associated with electroconvulsive therapy (ECT), which to their knowledge had not been previously reported. We described similar large upright T-waves during multiple monitored ECT (2). With multiple monitored ECT, four treatments are given during each anesthetic. In our patient, the T-waves became considerably larger than the QRS with each treatment. The T-wave changes subsided each time within minutes of the seizure before the next treatment. As Khoury and Benedetti reported, the T-wave changes we found resembled the intracranial injury pattern described by Burch and Phillips (3) rather than the narrow peaked T-waves associated with hyperkalemia. We also found no correlation with serum potassium levels. In addition, we measured serum creatine phosphokinase levels, which did not change.

An imbalance in sympathetic tone to the heart is believed to be the mediating mechanism in the electrocardiographic findings associated with central nervous system lesions (4). Furthermore, sympathetic imbalance has been implicated in other electrocardiographic changes associated with ECT (5), and we, like Khoury and Benedetti, attributed the large upright T-waves we observed to sympathetic imbalance. Stellate ganglion blockade and stimulation result in cardiac changes both in animals (6,7) and in humans (8).

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Iatrogenic Pharyngeal Pouch Mimicking Esophageal Atresia: A Diagnostic Challenge to the Anesthesiologist

Key Words: AIRWAY, PHARYNX. ANESTHESIA, PEDIATRIC. ANESTHESIA, OBSTETRIC.

To the Editor:

Topsis et al. (1) report three cases of esophageal perforation as a complication of neonatal resuscitation. Pharyngeal lacerations, however, may also follow breech delivery using the Mauriceau–Smellie–Veit maneuver—insertion of the obstetrician's finger into the mouth of the baby to facilitate extraction. The resulting iatrogenic pharyngeal pouch may mimic the symptoms of esophageal atresia and can even lead to an unnecessary thoracotomy (2,3). We report such a case.

A 3-kg male infant in breech presentation was vaginally delivered at 40-wk gestation to a 23-yr-old primipara. The head was delivered using the Mauriceau–Smellie–Veit maneuver. With initial mask ventilation, Apgar scores were 3 at 1 min and 8 at 5 min. Inability to pass a nasogastric tube and excessive foamy oral secretions led to the suspicion of esophageal atresia. A plain x-ray film showed the tip of the nasogastric tube above the level of the tracheal bifurcation. Gastrointestinal air was present. The patient was transferred to our institution, where an exploratory thoracotomy was planned.

After sedation with 5 μ g/kg fentanyl, nasotracheal intubation was performed on the second attempt using a Miller 0 blade and a 3.0-mm polyvinyl chloride endotracheal tube. Despite premedication with 0.1 mg atropine, copious amounts of foamy secretions made laryngoscopy difficult. A small mucosal laceration was seen on the posterior pharyngeal wall, which at that time was not considered

significant. Anesthesia was induced with 30 μ g/kg fentanyl in increments and atracurium. Ventilation was controlled using air in oxygen.

At thoracotomy the esophagus appeared normal and a 16F orogastric tube could be passed easily into the stomach. The symptoms were now attributed to the pharyngeal laceration, and a nasogastric tube was inserted using a laryngoscope. The postoperative course was uneventful. Oral feedings were begun on the seventh postoperative day. The baby was treated with antibiotics for 10 days and was discharged at 2 wk of age.

In conclusion, we describe a newborn infant with a iatrogenic pharyngeal pouch after breech delivery. Esophageal atresia was suspected, and an unnecessary thoracotomy was performed. Every baby scheduled for surgery because of suspected esophageal atresia should undergo careful examination of the pharynx at induction of anesthesia.

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Catecholamine Release During Isoflurane-Induced Hypotension

Key Words: ANESTHETICS, volatile—isoflurane. ANESTHETIC TECHNIQUES, hypotensive.

To the Editor:

We read with interest the article by Bernard et al. (1) on hypotensive anesthesia with isoflurane and enflurane. This paper confirms that isoflurane-induced hypotension in clinical practice is associated with normal cardiac output and that the decline in blood pressure is effected entirely through decrease in systemic vascular resistance, observations first reported in 1983 (2).

The data on plasma catecholamine levels and plasma renin activity are interesting and demonstrate that the sympathetic response during induced hypotension can be significantly different with different inhaled anesthetics at presumably equipotent concentrations. What is perplexing is that the changes in catecholamine levels were at variance with previously reported observations by Macnab et al. (3), who found that plasma norepinephrine levels did not increase and those of epinephrine actually decreased during isoflurane-induced hypotension. Difference in anes-

thetic depth and, consequently, the levels of hypotension may be a factor, as the blood pressure during hypotension was lower in the study of Macnab et al. (3). It is, however, difficult to compare the anesthetic depths because Bernard et al. did not indicate what inspired concentration was used to achieve the 1.3 MAC, nor did they mention how long the end-tidal concentration had been maintained when the sampling began at 15 min (T₁₅) after the start of the administration, and Macnab et al. did not measure endtidal concentrations. Irrespective of the anesthetic depth, the increases in plasma levels of catecholamines and renin activity during isoflurane-induced hypotension should be associated with rebound hypertension (3,4). Was this observed by Bernard et al.? Was the blood pressure significantly different between their two groups of patients at the end of the hypotensive period?

The observations of Bernard et al. may also represent a stress response to both hypotension and relative hypovolemia. Although the baroreceptor reflex is depressed less during isoflurane than during enflurane anesthesia (5), it is nevertheless a dose-related depression. This makes it difficult to understand why the levels of plasma catecholamines and renin increased further at 45 min (T_{45}) from T_{15} in the isoflurane group when the anesthetic depth could only have increased. Although a similar increase is reasonable in the enflurane group because blood pressure decreased significantly only at T₄₅, in the isoflurane group the blood pressures at T_{45} and T_{15} were almost identical. The timing of the increase in catecholamine levels suggests that hypovolemia may have been a significant factor, as confirmed by the low pulmonary wedge pressure. This interpretation does not invalidate the authors' findings of differences between the two inhaled agents, but it rather reconciles the conflict in the two quoted studies (1,3).

The findings of Bernard et al., coupled with those of Macnab et al., might lead one to conclude that (a) isoflurane-induced hypotension during normovolemia is not associated with catecholamine release, and (b) during mild to moderate hypovolemia, enflurane-induced hypotension is associated with less catecholamine release than isoflurane-induced hypotension. We concur that isoflurane is more appropriate than enflurane for induction of hypotensive anesthesia.

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In Response:

We concur with Drs. Lam and Manninen that hypovolemia during isoflurane hypotensive anesthesia may have accounted for increased plasma catecholamine levels in our study (1). Maintaining pulmonary capillary wedge pressure at a minimal level of 4 mm Hg did not exclude the possibility of hypovolemia during inhalation anesthesia. Inadequate analgesia may also be considered as a possible explanation. Our patients received only a single morphine injection as premedication. Because of the length of time between premedication and the last measurement (T_{45}), bone resection and femoral head removal may have resulted in pain and increased catecholamine release. However, plasma catecholamine concentrations had not increased significantly at T_{45} above the level at 15 min (T_{15}).

In a very similar study (2), we previously showed that no changes in plasma catecholamine concentrations occurred during isoflurane-induced hypotension in the presence of fentanyl. Likewise, in the study by Macnab et al. (3), catecholamine levels did not increase during isoflurane-induced hypotension. Finally, isoflurane-induced changes in plasma catecholamine levels depend on experimental design—not only on the isoflurane concentrations used and the level of hypotension, but also on surgical procedures (pain, duration) and the patients (e.g., age, cardiovascular diseases). Thus, comparisons between results can be inappropriate.

Most important, our results establish that catecholamine response under presumably similar operating conditions and depth of anesthesia was less marked during enflurane than during isoflurane hypotensive anesthesia. Despite increased plasma renin activity, we did not observe a rebound hypertension because as soon as the prosthesis was cemented in place isoflurane concentration was reduced to the normotensive level until closure of the skin.

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Conical Needles and Transdural Fluid Leak

Key Words: ANESTHETIC TECHNIQUES, SPINAL.

To the Editor:

The paper by Ready et al. (1) provides support for well-accepted clinical impressions such as "smaller needles make smaller leaks," as well as new data supporting the use of nonmidline approaches to dural puncture. Unfortunately, their concluding paragraph includes the following statement for which no support can be found in their data, "It would be advantageous to perform lumbar puncture with an approach permitting oblique angles with conical tips."

The authors tested a conical-tip needle (Whitacre) only in the 90° orientation. All oblique punctures were done with Quincke-type needles. To combine the benefits of obliquity demonstrated with one needle with the benefits of needle configuration demonstrated only at 90° is an excellent speculation that could well initiate a new experiment, but it is not good science for broadcast to the world.

I do not wish to differ with the authors. My own clinical experience, with only one known postlumbar puncture headache in over 300 paramedian lumbar punctures using the same 22-gauge Whitacre needle tested by Ready et al., strongly supports their speculation. I merely wish that they had tested the Whitacre needle at an oblique angle to demonstrate truly its superiority.

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Reference

 Ready LB, Cuplin S, Haschke RH, Nessly M. Spinal needle determinants of transdural fluid leak. Anesth Analg 1989;69:457–60.

In Response:

We would like to thank Dr. Noel for his comments related to our recent publication. He is correct in observing that our data do not confirm any advantage in using Whitacre needles at an oblique angle. We agree that the comment he has referenced is indeed speculation and that is what we intended it to be. We are interested to note that Dr. Noel's clinical observations support this speculation. Further study is required to determine what combination of factors (needle size, bevel design, angle of approach) results in the lowest rate of transdural leak.

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Decreased Oxygen Consumption During Anesthesia and Surgery: Decreased Metabolism or Oxygen Deficit?

Key Words: OXYGEN, consumption.

To the Editor:

In their report on the hemodynamic changes and oxygen (O_2) consumption occurring in burn patients undergoing surgery with enflurane or isoflurane anesthesia, Gregoretti et al. (1) note an approximately 55% decrease in minute O_2 consumption $(\dot{V}o_2)$ and a 70% decrease in cardiac output as compared with the preoperative control values in 15 anesthetized patients. The patients were said to be normothermic. Gregoretti et al. state that "whole body $\dot{V}o_2$ markedly decreased during anesthesia most likely because of decreased tissue metabolic requirements." However, decreased O_2 uptake can also be due to inadequate delivery of O_2 to peripheral tissues (tissue hypoxia) as well as to decreased metabolic requirements, and the difference between the two is important.

Waxman et al. (2) concluded that the decreased Vo₂ noted during anesthesia was due to inadequate O2 delivery rather than to decreased metabolic demands. They studied circulatory and metabolic parameters including lactate levels and Vo₂ in 12 high-risk patients undergoing major surgery under general anesthesia. Most received enflurane. They noted marked increases in lactate levels intraoperatively, which correlated with simultaneous decreases in Vo₂, but which did not correlate with mean arterial pressure or cardiac output. They attribute the decrease in Vo₂ to "impaired cellular utilization of oxygen, caused either by microcirculatory flow maldistribution, impaired oxyhemoglobin dissociation, or by a direct impairment of mitochondrial function." (2) Postoperatively, the patients' lactate levels remained elevated and correlated with the intraoperative "O2 deficit." This was defined as the product of the duration of surgery and the preoperative-intraoperative Vo₂ difference. This deficit was thought to cause the hyperdynamic postoperative circulatory state noted in these patients. Waxman et al. concluded that a reduced intraoperative Vo2 reflects primarily inadequate tissue oxygenation rather than simply decreased metabolic requirements despite attempts to maintain systemic blood flow. They suggest that lactate levels should be measured during metabolic studies as an index of cellular metabolism.

Gregoretti et al. did not measure lactate levels in their study; however, they state that the pH_a values were within normal limits intraoperatively during normocapnic ventilation. The postoperative increase in Vo_2 as compared with the preanesthetic baseline values reported in their patients when normothermic, not shivering, and treated with analgesics is similar to that noted by Waxman et al. (2). It suggests the occurrence of an intraoperative O_2 deficit rather than a decreased metabolic demand.

The correlations between cardiac output and $\dot{V}o_2$ noted by Gregoretti et al. (1) and between $\dot{V}o_2$ and O_2 deficit reported by Waxman et al. (2) do not prove a cause-and-effect relationship. However, the assertion that a decreased cardiac output (1) is a result of diminished tissue metabolism should be examined critically in view of the evidence for impaired tissue oxygenation (2).

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In Response:

Dr. Sosis contends that the decrease in whole-body oxygen (O_2) consumption $(\dot{V}o_2)$ observed during anesthesia in burn patients (1) resulted from an inadequate O_2 delivery or utilization rather than from decreased metabolic requirements. In our study anesthesia was associated with a 45% decrease in $\dot{V}o_2$ and a 30% decrease in cardiac output (CO) as compared with preoperative control values. The figures quoted by Dr. Sosis (i.e., a 55% decrease in O_2 and a 70% decrease in CO) are incorrect. Similarly, nowhere in our paper is it said that the patients were normothermic (see Table 2, where body temperature changes throughout the study are reported).

Dr. Sosis quotes the paper of Waxman et al. (2) to support his contention. These latter authors tested the hypothesis that "reduced intraoperative $\dot{V}o_2$ reflects inadequate tissue oxygenation rather than reduced oxygen needs; intraoperative elevation of blood lactate levels was used to identify the presence of anaerobic oxygenation." An intraoperative increase in lactate levels, in the 3–6 mEq/L range, led the authors to suggest that the reduced $\dot{V}o_2$ was due to inadequate tissue oxygenation. Further, as this inadequate tissue oxygenation occurred despite a CO maintained at preoperative values, they postulated an impaired cellular utilization of O_2 .

Besides tissue hypoxia (incidentally, one patient in the Waxman et al. series sustained an intraoperative cardiac arrest and eventually died), there are other factors, including catecholamine administration, respiratory alkalosis, and liver disease, which may explain the increased lactate (3–5) reported by Waxman et al. These authors (2) used an unspecified intraoperative therapy (catecholamines?) titrated to maintain CO at or above preoperative values. All their patients had abdominal surgery and presumably were mechanically ventilated. No arterial blood gases are reported, so it is unknown whether they were hypocapneic. Four patients, who had a portacaval shunt, presumably had cirrhotic liver disease. In addition, moderate intraoperative and postoperative increases in lactate blood levels

commonly occur due to an altered metabolism of glucose and its precursors, in turn, due to complex hormonal changes evoked by the surgical trauma (6). The increase in lactate blood levels reported by Waxman et al., therefore, does not prove that the anesthesia-induced decrease in $\dot{V}c_2$ is due to inadequate tissue oxygenation. Indeed, Waxman et al., in the discussion of their results, wrote: "An alternative explanation of these data is that lactate clearance decreases intraoperatively and that this, rather than lactate production, explains the increased levels. This alternative explanation cannot be excluded with the data available."

Dr. Sosis argues that the postoperative increase in $\dot{V}o_2$ as compared with preanesthetic baseline values observed in our patients suggests an intraoperative O_2 deficit. This argument is not tenable, as in our study the difference between preoperative and postoperative $\dot{V}o_2$ was neither statistically nor clinically significant.

The systematic studies of Theye and coworkers (7) have shown that the decrease in whole-body $\dot{V}o_2$ during inhalation anesthesia is mainly the result of the decreased $\dot{V}o_2$ of the heart, brain, and skeletal muscle, whereas the $\dot{V}o_2$ of the kidney and splanchnic area decrease to a lesser extent. Their data, corroborated by extensive literature recently reviewed (8,9), indicate that the decreased $\dot{V}o_2$ of the individual organs during inhalation anesthesia is due to decreased metabolic requirements rather than to inadequate oxygenation.

Our patients neither developed metabolic acidosis nor showed any evidence of organ or systemic damage in spite of an intraoperative $\dot{V}o_2$ of approximately 50% of preanesthetic values. In agreement with the literature above reported—and as it is difficult to envisage how an O_2 deficit equal to one-half of O_2 requirements can be sustained for 2–3 h without progressive metabolic acidosis and tissue damage—we considered the increase in $\dot{V}o_2$ most likely the result

of decreased metabolic requirements. Although we agree that during metabolic studies it may be desirable to measure lactate blood concentrations, we believe that increases in lactate blood levels, to be clinically significant, should be associated with a decrease in pH_a (10). As in our study no significant change in pH_a was noted, we doubt that lactate measurements would have changed our conclusion.

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Book Reviews

Handbook of Pediatric Intensive Care M. C. Rogers, ed. Baltimore: Williams & Wilkins, 1989, 448 pp, \$34.95.

This excellent handbook is an adaption of the encyclopedic *Textbook of Pediatric Intensive Care* and reflects the experience and expertise of its authors and editor at the Johns Hopkins University Hospital. The 24 chapters focus on problems commonly encountered in the pediatric critical care setting.

Clinical anesthesiologists will find the opening chapters on cardiopulmonary resuscitation and emergency airway management too simplistic. However, pediatric trainees with no special expertise in airway management will find the information quite useful.

Later sections on myocardial ischemia and cyanosis, pulmonary edema, adult respiratory distress syndrome, and the recognition and management of dysrhythmias are very strong. The section on shock in the pediatric patient is an excellent and pithy review of a complex problem. Neurologic problems in critically ill infants and children are systematically addressed in sections on the evaluation of coma and status epilepticus. Similarly, the chapters dealing with infectious diseases of interest to the pediatric intensivist are excellent. The remainder of the text covers organ system failure, diabetic ketoacidosis, and burns. Also included is a comprehensive 45-page formulary of drugs used in the pediatric intensive care unit.

The preface to the *Handbook of Pediatric Intensive Care* states that it is designed to serve as a reference "for the practical aspects at the bedside." The information is readily available. Numerous tables and illustrations help summarize material presented in the text. There are some annoying typographical errors and an occasional mislabeled figure caption, which the publisher will hopefully correct in the next edition.

There is a growing cadre of pediatrician-anesthesiologists who are involved in pediatric critical care. For many years, there was no single source of reference information for these individuals. The *Handbook of Pediatric Intensive Care* is practical and readable. Both practitioners and trainees will find it useful.

Scott R. Schulman, MD Department of Anesthesia School of Medicine University of California, Davis Sacramento, California Clinical Cases in Anesthesia A. P. Read and J. A. Kaplan. New York: Churchill Livingstone, 1989, 340 pp, \$29.95.

This book consists of discussions of 29 clinical cases divided among seven systems, such as respiratory, cardiovascular, and hematologic. The authors build on the question-and-answer format in each case using the traditional sequence of pathophysiology, pharmacology, preoperative evaluation, intraoperative management, and postoperative care. The challenge to the reader is first to attempt to answer each question and then to compare his or her answer to the one presented by the authors.

Unfortunately there are shortcomings to this basically admirable approach. The approach is fundamentally clinical, and, as such, the information is often "soft" with decisions often made on less-than-solid grounds. There is often no right or wrong answer, and this cannot be otherwise despite their use at times of basic science facts. So the reader is left with the dilemma of depending on the astuteness of the authors in making decisions for them. These decisions are judgment calls, if you will, which the reader may have to make in the operating room or to defend in the future before an examining board. Yet they will be often left without being adequately prepared for the inevitable next question "And why?" or "And why not?"

If the reader tries to make more of this text than a dogmatic "cookbook," he or she then must deal with an erratic bibliography. Some of the references are very old, some trivial, some generally inaccessible like the World Journal of Surgery. There are a number of topics that are obviously important and that are discussed at length in the text but for which there are no references at all.

Some discussions are incomplete, but this is to be expected, as the authors are not—and cannot be expected to be—experts in all areas. This is a wide-ranging text, far more inclusive than one would expect to find in a discussion of a simple collection of 29 clinical cases.

The authors relate the format of their text in passing to the oral examination of the American Board of Anesthesiology. But this resemblance is superficial, and the reader can only expect to derive a limited amount of help from this book in preparing for that examination. This is so because it is basically didactic in its approach despite the statements of the authors in their preface. Nevertheless, this text will probably find its widest sale to candidates for that oral examination. And if the various licensing bodies—state, federal, or even the ABA—continue to move in the same

direction as they seem to be doing now, then all of us, present diplomates included, will be purchasing books like this one.

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Preparing for the Anesthesia Orals

C. J. Gallagher and D. A. Lubarsky. Boston: Butterworth, 1989, 199 pp, \$29.95.

This manual will provide very limited help to board candidates facing the oral examination. At the same time the authors' arbitrary approach to problem-solving coupled with their dogmatic conclusions will frequently lead the reader astray.

This "how to" manual is divided into two sections. The first gives advice on 20 topics in 50 pages. These topics range from "What you're in for" and "What to read" to some specific subjects like "The machine age" (or how an anesthesia machine works) and "Vital signs." Whenever the topic leads to a discussion of basic science material, the authors frequently make errors. It is difficult to separate the occasional useful insights from the mistakes and errors of judgment. The second section consists of 20 case discussions, beginning with a short "guided case" (which the authors call the "stem question," a term more properly reserved for the written test format). They then build up from the guided case presentation a series of questions that the examiner might ask. These questions are followed by blanks, which the reader fills in and which are in turn followed by the authors' answers to those questions.

The positive aspects of this book can be briefly stated. For someone who has never taken the ABA oral examination the case discussions will provide a useful preview. But after an initial exposure there is little to be gained. The authors provide a few useful tips, but their value seems limited.

However, the shortcomings are considerable. The overwhelming use of jargon is a serious flaw. It sets no example to the readers as to how they should conduct themselves during the examination itself and may even lead them to use such language in the examination itself. Yet the authors are unquestionably proud of their "contribution" on this point. To this reviewer this book is the grossest example of the misuse of the English language in our specialty such as that recently described by Eger (1). One does not have to be a purist to make this criticism. One can make the same teaching point without such slang. Readability can certainly be achieved without it, and its use put this reviewer off. However, what are more important are the numerous factual errors sprinkled throughout the text. Most serious is the uncalled-for arbitrary approach that pervades the entire presentation and serves the reader ill. Finally the authors add a disclaimer that "These questions are meant to resemble board questions. Any verbatim reproduction of an actual board question is coincidental." Perhaps this is so, perhaps.

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Reference

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Common Problems in Obstetric Anesthesia Sanjay Datta and Gerard W. Ostheimer, eds. Chicago: Year Book Medical Publishers, 1987, 496 pp, \$54.95.

This text sets out not to be a comprehensive textbook but to present "a selection of cases that suggest management techniques." The 66 contributors include 48 anesthesiologists, 12 obstetricians, two pediatricians, two psychologists, and one nurse. Each chapter is brief (6-12 pages long). Topics believed by the editors to be important are discussed by multiple authors of the same or different specialties. The topics of acid aspiration and pregnancyinduced hypertension are well served by this approach. Each topic is covered by three excellent, well-referenced chapters that complement each other well. The two chapters on surgery during pregnancy are excellent but both cover the same material. The multiple chapters on vaginal birth after cesarean delivery and preterm labor are redundent, and the chapters on diabetes and breech delivery provide incomplete coverage of these topics.

Overall, the quality of the writing is uneven, a problem that may have been exacerbated by the large number of contributors. The chapters on thromboembolic disease, disseminated intravascular coagulopathy, and postdural puncture headache are excellent. An excellent chapter on management of the obese parturient is erroneously entitled postoperative pain relief. The standard method for inducing general anesthesia in the parturient is described in 16 of the 29 chapters; a separate chapter covering this topic that was referred to in the other chapters would have decreased this redundancy. The author of the chapter on respiratory problems advocates general anesthesia for wheezing asthmatic patients but does not mention that tracheal intubation is a strong stimulus for bronchoconstriction or that uterine atony and bleeding problems are exacerbated by most bronchodilators. Some of the chapters are poorly referenced and present only the authors' practices.

Chapters discussing rapidly evolving areas of obstetric anesthetic practice are out of date. This includes the chapters on the cerebral and cardiovascular toxicity of local anesthetics, epidural anesthesia test doses, management of the retained placenta, and the neonatal behavioral effects of obstetric anesthesia.

Preexisting medical problems that are discussed are generally discussed well; however, several important con-

ditions have been omitted. The discussion of paraplegic parturients is excellent; however, multiple sclerosis and lower back problems are not discussed. The only cardiac diseases mentioned are mitral stenosis and Eisenminger's syndrome.

In summary, this text contains a few chapters that are excellent but a larger number that are merely adequate. Some preexisting medical conditions are well discussed, but more are not covered at all. The scant number of preexisting medical conditions mentioned is surprising in a text of the case-discussion format. The chapters on rapidly evolving areas of obstetric anesthetic practice are out of date. General anesthesiologists in need of advice for the management of specific obstetric anesthesia situations would be better served by the use of one of the comprehensive obstetric anesthesia textbooks.

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Technical Manual of Anesthesiology, An Introduction

James E. Heavner, Craig Flinders, Dennis J. McMahon, Tim Branigan, and J. Michael Badgwell. New York: Raven Press, 1989, 167 pp, \$26.00.

Currently most anesthesia technicians have no formal educational training. As stated in the foreword, the intent of this book is to provide an introductory text dealing with anesthesia equipment and supplies as well as basic safety issues. The book is targeted to anesthesia technicians as well as medical students, nurses, and physicians.

The authors largely achieve their goals in providing such a text. In general, the book reads evenly and does not prerequire an advanced medical background. By design, it does not go into great detail on each individual topic, but provides essential and basic information on a wide variety of topics. Its short length, 158 pages of text, will encourage quick reading.

The chapters deal with the role of the anesthesia aide or technician, the basic anesthesia setup, patient positioning, the anesthesia machine, airway equipment, breathing circuits, vascular access, circulatory monitoring, respiratory monitoring, other monitors, the STAT lab, medical gases, and the drugs used in anesthesia. References are provided for those interested in a more detailed and comprehensive discussion of each subject. There is no section consolidating information on the cleaning and sterilization of equipment. This is addressed for some equipment when it is discussed.

I had two minor disappointments. First, except for the circle system, there was no discussion of the other breathing systems although references were provided. Second, a section dealing with the basic principles of protecting oneself from occupational hazards such as blood contami-

nation would be of value to one just starting to work in the operating room.

Three errors were noted. The schematic on the front cover is upside down. "JCAHO" is referred to by its old acronym, "JCAH," and on page 19 in the paragraph on flowmeters "counterclockwise" should be "clockwise."

In summary, I recommend this book for anesthesia technicians, medical students, nurses, and beginning anesthesia residents. It is essentially a basic explicatory text that can introduce the subject to individuals both with and without medical backgrounds.

Jonathan Roth, MD Albert Einstein Medical Center Philadelphia, Pennsylvania

Critical Care Medicine: Cutting Edge Issues Volume 3, No. 2 of Problems in Anesthesia B. Chernow and J. D. Todres, eds. Philadelphia: J. B. Lippincott, 1989, \$25.00 single issue or \$60.00 for annual subscription of four issues.

Chernow and Todres are to be congratulated for having compiled a valuable critical care textbook of extreme interest and importance to anesthesiologists. Unlike many similar publications, the editors have concentrated on producing a body of information that is both new and important particularly to the practicing anesthesiologist. They have preserved the goal of this issue by restricting the chapters to those areas of critical care medicine that are both developing and important to anesthetic management of critically ill patients. In only a few instances are the chosen chapters compilations of already known information. The editors and authors make no value judgments; rather, the text is written with careful attention to detail and with excellent references following individual contributions. One criticism would be that in some instances the chapters are so full of information and references that at times reading the chapter is a tour de force and requires a great deal of effort and concentration. However, at the end of this process, the reader will be rewarded by having acquired much new information and a series of excellent original and review articles for further investigation.

It is always difficult to highlight specific chapters because this appears to undermine the importance and appropriateness of the others. However, chapters relating to the stress response in critical illness, acute stress-induced gastrointestinal hemorrhage, continuous arteriovenous hemofiltration and dialysis, and thrombolytic therapy in critical care are all worthy of special mention. In each of these the authors tackle current controversial problems, and present information in a well-informed and useful fashion. Controversies are not avoided, but the reader is presented with adequate amounts of information so that ultimately personal decisions on future treatment protocols are sug-

gested as they might be following a well-informed discussion among faculty colleagues.

Obviously, this is a useful and highly effective format of presentation, and it should appeal to a large number of readers.

Critical care medicine is a field of extreme importance to anesthesiology, and many textbooks fail because they either repeat in a supercilious fashion information that is already known or have to do specifically with those areas of interest to the anesthesiologist in the operating room. This text avoids these pitfalls and provides information of interest outside the operating room, in a fashion that does not denigrate the skills of well-trained anesthesiologists or the importance of their practice outside the operating room as it relates to the intensive care unit.

Another interesting feature of the text is the degree of attention paid to the pediatric patient and concerns relating to injury and technique. Also, the chapter on ethical dilemmas does not concentrate entirely on the adult and includes decisions relating to pediatric management in an appropriate fashion. As with most chapters relating to problems in ethical interpretation of patient management, the chapter purports to provide no answers but does suggest an appropriate framework on which to base discussions and decisions. Certainly, in a chapter of this nature, global commentary is appreciated rather than specific suggestions that may vary from state to state depending upon specific legislation and judicial history.

The text ends with two important chapters. One is on cocaine abuse and its importance to current critical care practice and the other is a well-written chapter on implications of the manipulation of cerebral blood flow in the critically ill patient.

In summary, I found this to be a timely, well-edited, and well-planned text that does indeed discuss cutting-edge issues in critical care medicine; most significant is that it addresses these issues in areas of importance to clinical anesthesiologists in all areas of specialization.

Philip B. Lumb, MB BS Department of Anesthesiology Albany Medical College Albany, New York

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Abram SE, ed. The Pain Clinic Manual. Philadelphia: J.B. Lippincott, 1990, 458 pp, \$29.50.

Atkinson RS, Boulton TB, eds. *The History of Anaesthesia*. (International Congress and Symposium Series No. 134), Park Ridge, N.J.: The Parthenon Publishing Group, 1989, 649 pp, \$118.00.

Benjamin B. Diagnostic Laryngology, Adults and Children. Philadelphia: W.B. Saunders Company, 1990, 177 pp, \$95.00.

Desmedt JE. Neuromonitoring in Surgery. (Volume 1 in Clinical Neurophysicology Updates), New York: Elsevier, 1989, 377 pp, \$155.25.

Dorrington KL. Anaesthetic and Extracorporeal Gas Transfer. New York: Oxford University Press, 1989, 274 pp, \$75.00.

Edmunds LH Jr, Norwood WI, Low DW. Atlas of Cardiothoracic Anesthesia. Philadelphia: Lea & Febiger, 1990, 287 pp, \$125.00.

Feldman S, Harrop-Griffiths W, Hirsch N. Problems in Anesthesia. Analysis and Management. Boston: Butterworths, 1989, 180 pp, \$34.95.

Guzman MF, Brown AH, Been M, Cook S, Wren C, Rickens D. Manual of Cardiorespiratory Intensive Care. Boston: Butterworths, 1989, 314 pp, \$29.95.

Hensley FA Jr, Martin DE. The Practice of Cardiac Anesthesia. Boston: Little, Brown and Company, 1990, 759 pp, \$36.50.

Montoyama EK, Davis PJ, eds. Smith's Anesthesia for Infants and Children. 5th ed. St Louis: C.V. Mosby Company, 1990, 948 pp, \$89.00.

Soni N. Anaesthesia and Intensive Care. Boston: Butterworths, 1989, 225 pp, \$80,00.

Stanton-Hicks M, ed. Pain and the Sympathetic Nervous System. Boston: Kluwer Academic Publishers, 1990, 251 pp, \$90.00.



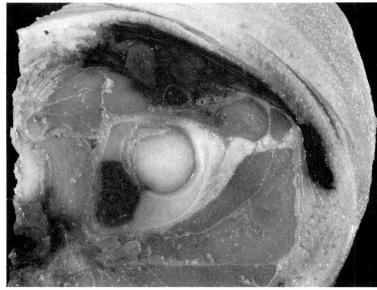
Errata

Wilson OB, Hamilton RF, Warner RL, Johnston CM, deFriece R, Harter L, Schweitzer C, Talaverra J, Hymel CM, Skolnick MH. The influence of Electrical Variables on Analgesia Produced by Low Current Transcranial Electrostimulation of Rats. Vol. 68, No. 5, May 1989, pp. 680, 681.

The authors wish to inform readers that the authors of Reference 14 should be Capel ID, Pinnock MH, Patterson MA. They also wish to inform readers that Reference 31 is Supplement 1 to Volume 33

Dalens B, Vanneuville G, Tanguy A. Comparison of the Fascia Iliaca Compartment Block With the 3-in-1 Block in Children. Vol. 69, No. 6, December 1989, p. 709.

The authors wish to inform readers that the caption appearing with Figure 3 is incorrect. The correct caption appears next to the figure below.



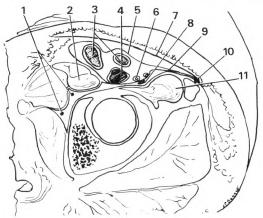


Figure 3: Transverse section at the root of thigh

- 1. Division branches of the obturator nerve
- 2. Pectineal muscle
- 3. Lymph nodes
- 4. Femoral vein
- 5. Femoral sheath
- 6. Femoral artery
- 7. Fascia lata
- 8. Femoral nerve
- 9. Fascia iliaca
- 10. Lateral cutaneous nerve of the thigh
- 11. Psoas muscle

A Guide for Authors

Manuscripts should be sent to:

Nicholas M. Greene, MD Editor in Chief Anesthesia and Analgesia Yale University School of Medicine 333 Cedar Street, New Haven, CT 06510

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All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Only one copy of an article not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96: 766-71 and *Lancet* 1982;284:1766-70.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, by parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

- □ Original articles describe in 3000 words or less clinical or laboratory investigations.
 □ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.
 □ Technical communications are papers that deal with instrumentation and analytic techniques.
- ☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.
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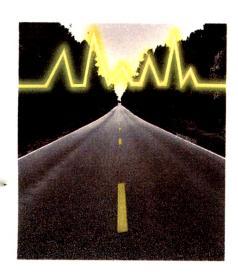
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☐ Discussion: Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not com-	 ☐ Submit three complete sets of figures. Figures should be in black and white only and professionally drawn and photographed; freehand o typewritten lettering is unacceptable. Note: Art work of published articles will not be returned. ☐ Instead of original drawings, roentgenograms, or other materia 				
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seven or more, list only the first three and add et al.) You CH, Lee KY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980; 79:311-4	Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the star of the article.				
 Personal author(s) books and monographs Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406. Chapter in a book Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Patho- 	 Consult the following sources for abbreviations: CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and O'Connor M, Woodford FP. Writing scientific papers in English an ELSE-Ciba Foundation guide for authors. Amsterdam: Else- 				
logic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.	vier-Excerpta Medica, 1975.				
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Brief SummaryThis drug should be used only by adequately trained individuals familiar with its actions, characteristics, and

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

CONTRAINDICATIONS: ITACRIUM IS CONTRAINDICATED IN PARENTS KNOWN TO NAVE A HYPERSISTAVITY TO IT.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION, ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Trachium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be

Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS:

General: Atthough Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazarious (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administed slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not controlled by braches and appropried by many anesthetic agents or varial stimulation. As a result, brachezerda.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many neisthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis. Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially tatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develope in the absence of estatished triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium did not trigger this syndrome. did not trigger this syndrome.

Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.

The safety of Tracrium has not been established in patients with bronchial asthma.

Long-Term Use in Intensive Care Unit (ICU): Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered

blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is with enterpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents. Itilite information is available on the plasma levels or clinical consequences of atracurium netabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite following long-term (days to weeks) infusion of Iracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in human have not been demonstrated. The effects of hemodalysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown.

Prun Interactions: Druss which may enhance neuromuscular blocking action of Tracrium include, enflurane,

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include, enflurane, isoflurane, halothane, certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

a patient has received from sometiment of Fertility. A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

Pregnancy: Peratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that torceps delivery will be necessary may increase. Fractium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tractium in any of the newborn infants, although small amounts of Tractium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium suitate, the reversal of neuromuscular blockade may be unsatisfactory and Tractium dose should be lowered as indicated.

Autoins Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

important adverse reactions was 77875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hermodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31% or 5.05 mg/kg of Tracrium, mean arterial pressure increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

Description: The patients of the patients of

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately Smillion patients given Traccuus the following adverse reactions are among the most frequently reported. General altergic reactions (anaphylactic or anaphylactic) which, in rare instances, were severe (e.g., cardiac arrest) Musculoskeletal: inadequate, prolonged block. Cardiovascular: hypotension, vasodilatation (flushing), tachy cardia, bradycardia. Respiratory: dyspnea, bronchospasm, laryngospasm; Integumentary: rash, urticaria, iniection site reaction

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

Payne J: Atracurium, Semin Anesth 1984;3:303-311

Region S. Anadomini, General Michael 1994, 3 903-311.
Basta S., Alir L. Savarese J. Clinical pharmacology of atracurium besylate (BW 33A): A new nondepolarizing muscle relaxant. Anesth Analg 1982, 61:723-729.

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273 K/D

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The University of California, Los Angeles Department of Anesthesiology has faculty positions available for individuals specifically interested in obstetric anesthesia. Duties include teaching and patient care. Evidence or promise of research productivity and scholarly writing desirable. Other requisites include California medical license or eligibility and ABA certification or in process. Address correspondence with five references and curriculum vitae to Kenneth A. Conklin, M.D., Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action/Equal Opportunity Employer.

316 L/E

BC or BE MD to join group of 3 MD anesthesiologists and 4 CRNAs, in the practice of anesthesia, intensive care, and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330. 345A/F

OHIO Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity/affirmative action employer.

Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

337A/F

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354B/G

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359B/G

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365C/E

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Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant. Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum 44 page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212)685-5010, FAX: (212) 685-6126.

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366CD

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372CD

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381CD

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397DE

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401DE

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394D/F

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392D

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Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma creations and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames Saimonella typhimum metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, in do detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman. Podiatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently

available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity, Delayed respiratory arest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halethane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of affentant induction, and by the type of surgery, e.g., nausea and vomitting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal Nausea Vomiting	28 18	44 31	14 11	5.	0 13	22 17
Cardiovascular Bradycardia Tachycardia Hypotension Hypertension Arrhythmia	14 12 10 18 2	7 12 8 13	39 7 30 5	0 36 7 20 4	31 0 6 6	0 11 0 0
Musculoskeletal Chest Wall	17	12	0	0	0	0
Rigidity Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory Apnea Postoperative Respiratory Depression	7 2	0 2	0	0	0	0
CNS Dizziness Sleepiness/ Postoperative	3 2	5 8	0 2	0	0	0.
Sedation Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and tiching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravengus LD₈₀ of ALFENTA is 43.0-50.9 mg/kg in guinea pips and 69.5-875 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability. In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm

agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. fo



March 1987, April 1988 U.S. Patent No. 4,167,574 49-7619902-M

Piscataway, N.J. 08854

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Anesthesia and Analgesia

Journal of the International Anesthesia Research Society Oldest Publication in the Specialty—Established 1922



In neuromuscular blockade

Norcuron (vecuronium bromide) for injection

Minimizes the variables



 ○ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease^{1,2}



∇ NORCURON* requires no dosage adjustments to avoid histamine release



May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment³⁴

As with all drugs in this class, NORCURON* should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Norcuron (vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS ORUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron* is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, DXYGEN THERAPY. AND REVERSAL AGENTS ARE IMMEDIATELY AWAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the amyasthenic (Eaton-Lambert) syndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral lampar that the profound stream of the profound profound stream of the profound profound stream. nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle

relaxants.

**PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity **reactions such as bronchospasm. flushing, redness. hypotension, lachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

**Renal Fallure: Norrouron's is well tolerated without clinically significant prolongation of neuro-muscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuro-muscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norrouron's should be considered.

**Altered Circulation Time: Conditions associated with slower circulation time in constitutes as delaying one dietax of long in time in prepared volume of distribution may contribute in a delaying one them. Therefore diesane should not be

states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not b

**Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron* metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

recommendations in patients with impaired liver function.

Long-term Use in L.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wear such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance. hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may not which may one consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-nisk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SuCH AS USE OF A PERIPHERAL NERVE STIM-ULATOR. TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE. MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease. Patients with severe obesity or neuromuscular cisease may pose airway and or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron³.

Norcuron* Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially stall hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capable of triggering malignant hyperthermia. C. N.S.: Norcuron* has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Orug Interactions: Prior administration of succinyicholine may enhance the neuromuscular blocking effect of Norcuron* (vecuronium bromide) for injection and its duration of action if succinyicholine is used before Norcuron* the administration of Norcuron* should be delayed until the succinyicholine effect shows signs of wearing off. With succinyicholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* may be administered to produce complete neuromuscular blocks with clinical duration of action of 25-30 minutes. The use of Norcuron* before succinyicholine, in order to attenuate some of the side effects of succinyicholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron*, therefore these drugs and Norcuron* may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron* will enhance neuromuscular blockade.

Other nondepolarizing neuromuscular blocking agents act in the same tashion as does Norcuron*, therefore these drugs and Norcuron* may maintest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron* will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron* may she the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral-intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis, aminoglycosides (such as neomycin, streptomycin, knammycin, gentamicin, and chilydostreptomycin); tetracyclines; bactracin, polymyxin B; colistim; and sodium colistimethate.

Other: Experience concerning injection of quinicine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat): Ectrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to after neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxema of pregnancy, may enhance the neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the magnenis, inhalamement of fertility: Long-term studies in animals have no

nitrous oxide, or droperious. See OVERDOORGE to Business of the Control of the Control oxide of the Control oxide oxide

OVERDOSAGE: The possibility of latrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron* produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron* as with other neuromuscular blockase; This may be manifested by skeletal muscle weakness, decreased respiratory reserve; low tidal volume, or apnea. A peripheral rerve stimulation may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve. I will not other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regional, Gyridostignine bromide) injection, neostignine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually natagonize the skeletal muscle relaxant action of Norcuron. Sustificatory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such origination is assurable in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such promises the management is the same as that of prolionage neuromuscular blockade or out offer the supervision of experienced clinicians

anesthetics and by prior use of succinylcholine (see PRECAUTIONS Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. To obtain maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of

anesthetics and by prior use of succinvicholine (see PRECAUTIONS: Crug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. To obtain maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of muscle twich response to peripheral nerve stimulation is advised. The recommended initial dose of Norcuron* is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₉₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron* is enhanced. If Norcuron* is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron* dose may be reduced by approximately 15%, i.e. 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron* If intubations is performed using succinylcholine, a reduction or initial dose of Norcuron* to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

Ouring prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron* are recommended. after the initial Norcuron* injection, the first maintenance doses will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron* lacks clinically important cumulative effects. subsequent maintenance doses of our 0.00 mg/

Infusion rates of Norcuron* can be individualized for each patient using the following table:

Drug Delivery Rate	li .	nfusion Delivery Rate	
(µg/kg/min)	0.1 mg/mL*	(mL/kg/min) 0.2 mg/mL†	
0.7	0.007	0.0035	
0.8	0.008	0.0040	
0.9	0.009	0.0045	
1.0	0.010	0.0050	
1.1	0.011	0.0055	
1.2	0.012	0.0060	
1.3	0.013	0.0065	

10 mg of Norcuron in 100 mL solution †20 mg of Norcuron* in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump. NORCURON* INFUSION RATE - mL/MIN

Amount of Drug		Patient Weight – kg					
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
09	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0 44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1 04	1.17	1 30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS) titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children.

usage in remaids (see Procum) months in the area is sunful therefore, no losing recommendation can be made.

COMPATIBILITY: Norcuron* is compatible in solution with.

0 9% NaCl solution
5% glucose in water
Sterile water for injection

5% glucose in saline Lactated Ringers

Use within 24 felie water for injection
Use within 24 felie water for injection
Use within 24 felie water for injection
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration
whenever solution and container permit
\$TORAGE: 15 and (59-86°F). Protect from light

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

 When reconstituted with sterile water for injection or other compatible I.V. solutions. Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

 REV. 3.89

- References:

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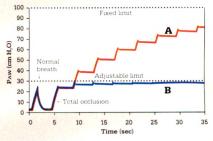
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FOR SHORTER SURGICAL Rapid-acting PROCEDURES: (alfentanil HCI) Injection (I THE ALFENTA For moment-to-moment ADVANTAGE control of stress responses RAPID ONSET Rapidly blocks sympathetic responses to induction *As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of and intubation 10 50 SHORT DURATION Results in quick recovery 45 * respiratory depression and increased airway resistance usually increase with dose, but 15 of consciousness* have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the 40 20 RAPID RECOVERY Postoperative respiratory depression is of short tient must continue well patient must after surgery. duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 up per mil of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isofonicity, has a pit range of 4,0-6,0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersonstitivity to the druin.

sodium chloride for isotoricity, has a pit range tin a u-o u.

CONTRAINDICATIONS: A LENTA (altentani hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA (altentani hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY DEFECTS OF POTENT OPIDIOS. AN OPIDIO ANTAGONIST RESUSCITATIVE AND INTUBATION EQUIPMENT AND DY'GEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBLITY OF DELAYED RESPIRATORY DEPRESSION. MONITORING OF THE PATRENT MUST CONTINUE WELL AFTER SURGERY ALFEATA (altentani hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages above 130 µg/kg will consistently produce muscular rigidity with an involves all skeletal rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles including those of the neck and extremities. The incidence may be reduced by 11 troutine methods of administration of neuromuscular blocking agents for balanced onoid anesthesis; 20 administration of 12 february dose of a neuromuscular blocking agent should be displayed administration of ALFENTA at dosages up to 130 µg/kg. following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be appropriate for the patient's cardiovascular status. Adequate facilities should be administration of ALFENTA is used in rapidly administred anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent when ALFENTA is used in rapidly administred anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent when ALFENTA is used in rapidly administred anesthetic dosages (above 130 µg

PRECAUTIONS: DELAYED RESPIRATION DEPIRESSION, RESPIRATION THEREFORE, VITAL SIGNS MUST BE MONITORED
ARRHYTHMAS AND HYDOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED
CONTINUOUSLY.

General: The initial dose of ALFENTA (altentanil hydrochloride) should be appropriately reduced in elderly and
debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese
patients (more than 20% above idial total body weight), the dosage of ALFENTA include be determined to
papierance of delta waves in EEG, was 40% lower in genature patients than that needed in healthy young patients
in patients with compromised liver function and in genatic patients, the plasma clearance of ALFENTA may be
reduced and postoperative recovery may be prolonged, induction doses of ALFENTA should be administered slowly
lover three minutes). Administration may produce loss of vascular fone and hypotension. Consideration should be
given to fluid replacement prior to induction. Disagrapm administered immediately prior to or in conjunction with
high doses of ALFENTA may produce vasoidation, hypotension and result in delayed recovery. Bradycardia produced
by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with
atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relation
and conventional resuscitative methods. The hemodynamic effects of a particular muscle relation
apart. Following an anesthetic moduction dose of ALFENTA, requirements for volatile inhalation anesthetics or
ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion
analgents can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression
hould be discontinued at least 10-15 munitors prior to the end of surgery. Respiratory depression, appropriate by poind
analgencs can be revised by opioid antagonists such as n

respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA. Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other (NS depressants such as barburtuates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or protonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for votatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of protonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and protong recovery.

renoperative administration to drugs affecting nepatric blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of FertiHity: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominismal tebral test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal nutations. The Ames Salmonella hyphimunium metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 25 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal foxicity (decreased food consumption with increased mortality) following prolonged administration of her drug No evicence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported, therefore, use in labor and delivery is not recommended.

Nursing Mathers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman. Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opinids. See CLINICAL PHARMACOLLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity, Delayed respiratory areas, that dycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 755 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane, incidences are based on disturbing and endisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported modence in clinical trials of affentant induction, and by the type of use, e.g., chest wall rigidity has a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal		***************************************		-		
Nausea	28	44	14	5 9	0	22
Vomiting	18	31	11	9	0 13	17
Cardiovascular						
Bradycardia	1.4	7	8 39	Û	0	0
Tachycardia	12	12	39	0 36 7	31	11
Hypotension	10	12 8 13 2	7	7		0
Hypertension	18	13	30 5	20	0 6	0 0 0
Arrhythmia	2	2	5	4	6	Ô
Musculoskeletal						
Chest Wall	17	12	0	0	0	0
Rigidity						
Skeletal Muscle	6	2	6	2	0	0
Movements						
Respiratory						
Apnea	7	0 2	0	0	0	0
Postoperative	2	2	0	0	0	0
Respiratory						
Depression						
CNS						
Dizziness	3 2	5 8	θ 2	0	0	0
Steepiness/	2	8	2	0	0	0 6
Postoperative						
Sedation						
Blurred Vision	2	2	0	Q	0	0

From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

From two conticat trials, one involving supplemented balanced barburate (introus oxide anesthesia and one in healthy voluniteers who did not undergo surgery.
In addition, other adverse reactions less frequently reported (1% or less) were, Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative eighteria, hypercarbia, pain or injection, urticana, and iching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
ADRUG ABUSE AND DEPENDENCE: ALFENTA (affentant hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
DYERDUSABE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA affentant hydrochloride) is see CLINICAL PHARMACOLOGY: as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during chinical trials. The intravengus LDs, of ALFENTA is 43.0-6.9 mg/kg in quieze pips and 59.5-86.75 mg/kg in dogs. Intravenous administration of an opioid antagonist such as natioxine should be employed as a specific antidate to manage respiratory depression. The duration of respiratory depression following overtosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist such as national propersion of the opioid antagonist such as national propersion of the opioid antagonist and propersion of a patent arraw, administration of overgen, and assisted or controlled ventilation is undecated for hypoventilation or agine. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to fractiate assisted or controlled ventilation. Intravenous fluids and visualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% aboud be

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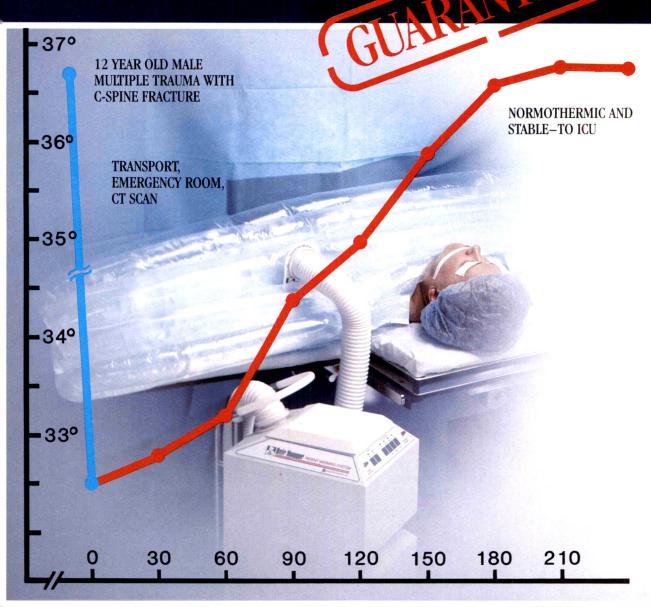
Anesthesia and Analgesia

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Before prescribing, please consult complete prescribing information, of which the following is

CAUTION: Federal Law Prohibits Dispensing Without Prescription.
DESCRIPTION: SUFENTA (sufentanii citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl-1-[-2-(2-thienyl-)thyl]-4-pierdinyl-N-pierdylopanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanii citrate equivalent to 50 µg per ml of sufentanii base for intravenous injection. The solution has a pH range

of 3,5-9.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extender postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of
intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid
antagonist, resuscitative and intubation equipment and oxygen should be readily available.
SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of
muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset
than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck
and extremities. The incidence can be reduced by: 1) administration of up to ½ of the full paralyzing dose of a nondepolarizing neuromuscular blocking egent just prior to administration of SUFENTA at dosages of up to 8 µg/Kg,
2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when
SUFENTA is used in anesthetic dosages (above 8 µg/Kg) titrated by slow intravenous infusion, or, 3) simultaneous
administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in
rapidly administered anesthetic dosages (above 8 µg/Kg). The neuromuscular blocking agent should be compatible
with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and
eventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all
degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated
patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be

Degrees or respiratory operpession.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxant nequired should be considered in the selection of a neuromuscular blocking agent. High doses of particuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opinid analogismist such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opinidal analogism of a maintained. As with all potent opinids, profound analogism is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the post-operative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquitzers, other opinids, general anesthetics or other CNS depressants. In such patients, opinida may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration; Impaired Repatic or Renal Function; In patients with liver or kindey dysfunction, SUFENTA should be administered with caution due to the importance of these organs in th

Garcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no

structural chromosome mutations. The Ames Salmonella typhimurium metabolic activating test also revealed no

mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects mem by probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous L0₅₀ of SUFENTA in 516.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal AUVENTS: REAU TIONS: In emost common adverse reactions of opinios are respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest vall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were: Cardiovascular: tachycardia, arrhythma Castrointestinal: nausea, womiting Central Nervous System: chills Miscellaneous: intraoperative muscle movement

DRIDG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravengus LO_{go} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LO_{go}s in other species). Intravengus LO_{go} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LO_{go}s in other species). Intravengus administration of an opioid antagonist such as naloxone should be employed as a specific antidate to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hyporentiation or a pinea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed. DRUG ABUSE AND DEPENDENCE: SUEENTA (sufentanil citrate) is a Schedule II controlled drug substance that

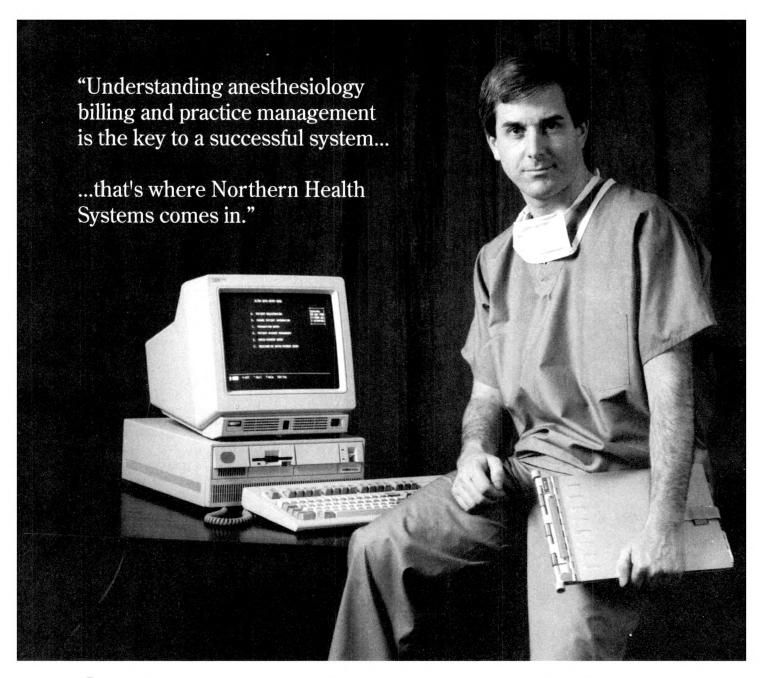
hypotension and other supportive measures may be employed.

DOSABE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, hypotension such underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C [559-86° E].

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Please see summary of product information on adjacent page. Copyright © 1990 by Hoffmann-La Roche Inc. All rights reserved. References: 1. Roche Scientific Summary. The Evaluation of VERSED* (brand of midazo am HCI/Roche) & Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, New Jersey, 1986. 2. White PF. Anesthesiology, 1982;57:279-284. 3. Data on file (Abs. #069-005), Hoffmann-La Roche Inc., Nutley, New Jersey.

VERSED⁴ (braind of midazolam HCI/Roche) (VINJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious aedation. In some cases, where tally areas, properties and seed of the se or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
The initial intravenous dose for conscious sedation may be as fittle as 1 mg, but

should not exceed 2.5 mg in a normal healthy adult. Lower does are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doese. should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1mg/mL formulation or dilution of the 1mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product informatten under DOSAGE AND ADMINISTRATION for complete dosing information

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzoduzpines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy. WARNENGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxida/oardiac arrest unless effective countermeasures are taken manufactable. Vittal damp should existed to be predictioned during the process profest. Immediately. Vital signs should continue to be monitored during the recovery pericd. Because IV VERSED depresses respiration, and optoid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventillation, maintaining a patent alrway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the con-

patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, sicohol or other CNS depressants may increase the destination of the proceeding of the proceeding of the processing of the processin

risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renel failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, come, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anes-

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the atient of the potential hazard to the fetus.

patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia

etion for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an Increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous injection of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your

physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication,

VERSED® (brand of midazolam HCI/Roche) INJECTION

particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of

halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered

Although the possibility of minor interactive effects has not been fully studied, VERSED Arthough the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in pattents without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylchofine and nondepolarizing muscle relevants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mulagenesis, impeirment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarity be of single or several doses. Midazolam did not have mutagenic activity in tests that were conducted. A reproduction study in rate did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delikery: Use in obstatrics has not been evaluated. Because midazokam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM Injection: headache (1.3%); local effects at IM site: pain (3.7%), induration. (0.5%), reciness (0.5%), muscle stiffness (0.3%). Following IV administration: hiscoughs (3.5%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tendemess (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), philebitis (0.4%). Other effects (<1%) malnly following IV administration: *Resignatory*: Laryngospasm, brone-theospasm, brone-the chospasm, dyspneá, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. Cardiovascular: Bigeminy, premature ventricular contractions, vasovagai episode, tachycardia, nodel rhythm. Gastrointestinal: Acid taste, excessive sal vation, retching. CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, andety, grogginess, restlessness, emergence delir-ium or agitation, prolonged emergence from anesthesia, dreaming during emergence, ium or agration, protonged emergence from anextresia, dreaming ourning emergence, sleep disturbance, insomnia, nightmares, athretold movements, ataxia, dizziness, dysphonia, paresthesia. Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyellds, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, prufitus. Miscellaneous: Yawning, lethargy, chills, weakness, tooth-ache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzo-

diazapines (e.g., sedation, somnolence, confusion, impalied coordination, diminished reflexes, come, untoward effects on vital signs). No specific organ toxicity would be

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which DOGAGE AND Administration and Individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diszepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS SERIOUS AND LIFE-THREATENING CARDUNESMINOTY ADVENSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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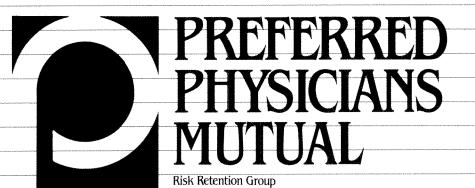
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*Nondepolarizing neuromuscular blocking agents.

TRACRUM INJECTION (atracurium besylate)

References and brief summary of full prescribing information can be found on the following page.

TRACRIUM INJECTION (atracurium besylate)

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Brief SummaryThis drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to tacilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR BROOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain intreshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such insistures. Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes latal. Tracrium Injection 5 mL ampuls and 5 mL single use vials 50 not contain benzyl alcohol. mL single use vials do not contain benzyl alcohol.

and other complications in newborn infants which are sometimes tatal. Tractrium injection 5 mL amputs and 5 mL single use valas to not contain benzyl alcohol.

PRECAUTIONS: General: Although Tractrium is a less potent histamine releaser than d-fubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tractrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release which any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tractrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tractrium has no clinically significant effects on heart rate in the recommended dosage range; it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tractrium than with other muscle releasants. Tractrium may have profound effects in patients with myasthenia gravis. Eaton-Lambert syndrome, or other neuromuscular diseases in which potential to a sessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or car-cinomatosis. Multible factors in anesthesia paractice are suspected of triggering adjents to brade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or car-cinomatosis. Multible factors in anesthesia part process or car-cinomatosis. Multible factors in anesthesia part process or car-cinomatosis. Multible factors in anesthesia particular disorders and particular disorders develop in the abse PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, women during delivery by cesarean section. No narmful effects were attributable to incommining on the newborn infants, although small amounts of Tractions were shown to cross the placental barrier. The possibility of depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatistactory and Tractium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tractium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not hepen established. month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 77875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vising changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increases in 1.1% of patients, while heart rate increased in 1.5% and decreased in 0.8% of these patients. Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently patients. Unserved in Linitizar Practice: Based on clinical experience in the 0.5, and the United kingdom approximately 3 million patients given Tractium the following adverse reactions are among the most frequently reported: General: allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest). Musculoskeletai: inadequate, prolonged block. Cardiovascular: hypotension, vasodilatation (flushing), tachycardia, bradycardia, Pespiratory: dyspnea, bronchospasm, laryngospasm; Integumentary: rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

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Editorial

Combining Evidence From Clinical Trials

Rebecca DerSimonian, sp

Key Words: STATISTICS, META-ANALYSIS.

The pooling of results from a series of clinical trials to evaluate the efficacy of a certain treatment for a specified medical condition is an attractive approach, one that is becoming increasingly popular in medical research. The approach is especially advantageous in clinical research where information on efficacy of a treatment is available from a number of different studies with similar protocols, each of which taken separately may either be too small or too limited in scope to come to generalizable conclusions about the effect of treatment. Combining the findings across such studies represents an attractive alternative for strengthening the evidence about the treatment efficacy. The report in this issue by Pace on 'Prevention of Succinylcholine Myalgias: A Meta-Analysis" (1) underscores the attractiveness as well as the popularity of the approach in clinical research.

Meta-analysis is a general term to describe the statistical analysis of a collection of analytic results for the purpose of integrating the findings. Pace utilizes one such meta-analytic technique, a random-effects model, to pool the results from 45 clinical trials to evaluate the efficacy of several drug regimens for the prevention of myalgias after succinylcholine therapy. Considered separately, the individual trials yield inconsistent conclusions: some studies imply a positive treatment effect; others indicate no effect. Summarizing the evidence in a random-effects model, Pace concludes that all but one of the drug regimens are prophylactic for myalgias.

The use of a random-effects model to summarize

the findings from a series of experiments is not new, and examples of the method's application are available from many areas of research including agriculture, education, and medicine (2–4). In clinical research, the basic idea of the random-effects approach is to parcel out some measure of the observed treatment effect into two independent and additive components, θ_1 and e_1 . θ_1 is the "true" treatment effect, the quantity of interest attributable to treatment in the *i*th trial, and e_i is the sampling error. In the review of the trials for myalgias prevention, Pace considers the model where the treatment-effect measure is the risk difference. Other effect measures, such as the risk ratio or the relative odds, can be similarly considered.

The true treatment effect associated with the ith trial, θ_i , will be influenced by several factors, including patient characteristics and design and execution of the trial. To account explicitly for the variation in the true effects, the random-effects model assumes θ_i is the sum of μ and δ_i . Here, μ is the mean effect for a population of possible treatment evaluations (which we would like to make inferences about) and δ_i is the deviation of the ith study's true effect from the population mean. The population variance, $var(\delta) =$ τ^2 , represents both the degree to which treatment effects vary across experiments and the degree to which individual trials give biased assessments of treatment effects. Regarding the trials at hand as a sample from this population of treatment evaluations, we can use the observed effects to estimate μ as well as τ^2 . DerSimonian and Laird present simple noniterative estimators for the relevant parameters in this setting (5).

For the myalgias prevention study, the estimates of μ and τ^2 suggest generally positive treatment effects as well as large population variance (heterogeneity of effects). The phenomenon of treatment-effect heterogeneity (even across carefully controlled ran-

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domized studies) is not uncommon and has been previously noted (5). Unless it is negligible, this heterogeneity should be accounted for and incorporated into the analysis of the overall efficacy of the treatment. The random-effects model allows us to quantify the degree to which the treatment effects vary across the trials and to incorporate this variation, however small, into the analysis. The method is approximate, and, in reality, the model assumptions may not completely hold. Nevertheless, the random-effects approach to meta-analysis of clinical trials is useful both in summarizing the data and in characterizing the distribution of treatment effects in a series of studies.

To allow for more specific therapeutic recommendations, it is clearly preferable to reduce the heterogeneity of treatment effects. If the effect of treatment depends on patient characteristics, τ^2 will naturally be large if the studies included different types of patients. In principle, we can extend the simple random-effects model to include pertinent covariates, and the corresponding τ^2 will be reduced. This is

often difficult in practice, however, because relevant covariate information may be missing for some trials (as it is in the myalgias prevention study). Improvement in standards for medical data gathering/reporting and further development of methods for handling missing covariate information are needed to strengthen our ability to combine results from clinical studies.

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Prevention of Succinylcholine Myalgias: A Meta-Analysis

Nathan L. Pace, MD

PACE NL. Prevention of succinylcholine myalgias: a meta-analysis. Anesth Analg 1990;70:477-83.

Meta-analysis is a term used to describe statistical methods for evaluating a series of research reports; this analysis transcends the limitations that may be inherent in each of the individual studies summarized. Forty-five research reports of clinical trials for the prevention of myalgias after succinylcholine were assembled. Four classes of preventive drugs (nondepolarizing muscle relaxants, benzodiazepines, succinylcholine in "self-taming" doses, and local anesthetics) were reported in detail sufficient to allow for inclusion in a meta-analysis of clinical efficacy. Each study was summarized by determining the difference in the incidence of myalgias on the first postoperative day between treatment

and control groups. A random-effects variance components approach was used. Seven meta-analyses were performed (atracurium, d-tubocurarine, gallamine, pancuronium, diazepam, succinylcholine in self-taming doses, and lidocaine). For each meta-analysis there was statistically significant heterogeneity among studies. Atracurium, d-tubocurarine, gallamine, pancuronium, diazepam, and lidocaine all significantly decreased the frequency of myalgias by about 30%. Succinylcholine in self-taming doses alone was not efficacious.

Key Words: STATISTICS, META-ANALYSIS. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE.

There exists a host of anesthetic side effects that contribute to patient morbidity. One of these, postoperative myalgias after the administration of succinylcholine, was recognized and reported soon after the introduction of succinylcholine into clinical practice in the 1950s. An extensive literature on this subject has since developed, with researchers reporting the results of many small- to medium-sized clinical studies using various drugs to lower the incidence of myalgias. The drug prophylaxis most commonly recommended has been the administration of a small dose of nondepolarizing muscle relaxant, the "pretreatment" or "defasciculating dose." Some studies have shown positive results, i.e., fewer and less severe myalgias, and some studies have failed to show a treatment effect. With their inconsistent findings, it has been difficult to summarize with certainty these diverse research studies.

Data analysis can be divided into three categories (1): primary analysis, the original analysis of an experiment; secondary analysis, reanalysis of research data with better statistical tools or with dif-

ferent questions; and, third, meta-analysis, a systematic approach for summarizing quantitatively through statistical methods the results of a large number of previous studies. Interestingly, the earliest meta-analysis has been attributed by Sacks et al. (2) to the anesthesiologist Henry K. Beecher, in his 1955 study of placebo responses (3). Since then, however, meta-analysis has been little used to combine and interpret the research reports of anesthesia. Only one report has been published (4).

The considerable number of small- to mediumsized clinical studies exploring the pharmacologic prevention of myalgias associated with the use of succinylcholine have failed to show consistently the efficacy or nonefficacy of preventive drugs, including nondepolarizing muscle relaxants, local anesthetics, benzodiazepines, and small "self-taming" doses of succinylcholine. This report uses meta-analysis to review the extensive literature evaluating the pharmacologic prevention of succinylcholine-induced postoperative myalgias.

Methods

The methodology suggested in three recent reviews of meta-analysis was followed (2,5,6). A Medline literature search for English-language reports con-

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cerning succinylcholine and postoperative myalgias in humans since 1966 was performed. The bibliographies of these papers were examined for additional similar reports; the reference lists of relevant chapters of current textbooks of anesthesia were also searched. No abstracts or reports of meeting presentations were included; no attempt was made to obtain unpublished studies. All reports were classified as to study design by the classification scheme described by Bailar et al. (7). Papers reporting a comparative clinical trial of a drug therapy to reduce the incidence of postoperative myalgias after succinylcholine were collected for analysis. To avoid selection bias, papers were selected for analysis only on the basis of study design, not study results. A log of all references uncovered by the literature search and their acceptance or rejection for analysis was maintained.

Each paper was reviewed three times by the investigator to reduce the chance of data-extraction error and bias. The following information was sought and abstracted as available from each report: numbers of treatment groups; study drugs and their routes of administration and dosages; numbers of patients in each treatment group, together with gender, surgery type, ranges of ASA physical status scores, and ranges of and mean ages; methods of allocation of patients to treatment group; use of patient/investigator blinding; ambulatory status of patients; methods for quantification of myalgia; drugs used for induction of anesthesia; dose of succinvlcholine; interval between the administration of the study preventive drug and the administration of succinylcholine; and the number of patients with myalgia on the first postoperative day. This broad range of patient characteristics and perioperative variables was sought so as to allow inclusion of covariates in the statistical model and thereby reduce the heterogeneity of drug effect.

All drugs for which four or more studies testing pretreatment efficacy had been published were combined for statistical analysis. The study outcomes of interest were the proportion of patients in the treatment and control groups experiencing muscle aches and pains on the first postoperative day. Within each study, multiple control groups and multiple dose treatment groups (receiving the same drug) were combined for analysis. If n_{T_i} and n_{C_i} were the number of patients in the ith study treatment and control groups, respectively, and if x_{T_i} and x_{C_i} were the number of treatment and control patients reporting first postoperative day myalgias, respectively, then $r_{T_i} = x_{T_i}/n_{T_i}$ and $r_{C_i} = x_{C_i}/n_{C_i}$ were the treatment group and control group response rates. For each study, the specification of the observed treatment effect was summarized by the risk difference $y_i = r_{C_i} - r_{T_i}$; this was the absolute difference in frequency of outcome between treatment and control groups. The sampling variance of the *i*th study was estimated by $s_i^2 = r_{T_i} (1 - r_{T_i})/n_{T_i} + r_{C_i}(1 - r_{C_i})/n_{C_i}$.

A random-effects variance components approach proposed by DerSimonian and Laird was used for the statistical analysis (8). The observed treatment effect (risk difference) was parcelled out into two additive components, the true treatment effect θ_i and the sampling error e_i ; in turn, the true treatment effect θ_i was divided into a mean population effect μ and a deviation of the ith study's effect, δ_i , from the population mean. The model equation was $y_i = \theta_i + e_i = \mu + \delta_i + e_i$. Risk differences were compared to check for homogeneity by graphical inspection (5) and by a χ^2 statistic

$$Q_w = \sum_{i=1}^k w_i (y_i - \overline{y}_w)^2,$$

where

$$\overline{y}_{w} = \sum_{i=1}^{k} w_{i} y_{i} / \sum_{i=1}^{k} w_{i},$$

k is the number of trials being combined, and $w_i = 1/s_i^2$ (8). The results were pooled to perform a noniterative estimation of the variance between studies,

$$\Delta_{w}^{2} = \max \left\{ 0, \left\{ Q_{w} - (k-1) \right\} \middle/ \left[\sum_{i=1}^{k} w_{i} - \left(\sum_{i=1}^{k} w_{i}^{2} \middle/ \sum_{i=1}^{k} w_{i} \right) \right] \right\},$$

the mean risk difference across studies

$$\mu_{w} = \sum_{i=1}^{k} w_{i}^{*} y_{i} / \sum_{i=1}^{k} w_{i}^{*},$$

where $w_i^* = (w_i^{-1} + \Delta_w^{-2})^{-1}$, and the asymptotic standard error of the mean risk difference

$$SE(\mu_{\mathbf{w}}) = \left(\sum_{i=1}^{k} w_i^*\right)^{-1/2}$$

(8). The null hypothesis of no treatment efficacy (μ = 0) was tested by a z-score confidence interval (8). The noniterative method proposed by DerSimonian and Laird did not provide a test to compare the treatment effect between sets of meta-analysis, for example, pancuronium versus lidocaine or diazepam versus curare. Assuming that the mean risk difference estimated for each meta-analysis was normally distributed with a known variance, the principle of generalized likelihood (9) allowed the creation of a χ^2 test statistic,

$$\chi_{j-1}^2 = \sum_{i=1}^j \left(\frac{\tilde{x}_i - \tilde{x}}{\sigma_i}\right)^2$$

to compare several meta-analyses, where $\bar{x}_i = \mu_w$ from the *i*th meta-analysis, j is the number of meta-analyses,

$$\ddot{\mathbf{x}} = \sum_{i=1}^{j} \tilde{\mathbf{x}}_i / \sigma_i^2 / \sum_{i=1}^{j} 1 / \sigma_i^2,$$

each $\bar{x}_i \sim N(\mu_I, \sigma_i^2)$, and $\sigma_i^2 = \{SE(\mu_w)\}^2$ from the *i*th meta-analysis. A two-sided $\alpha < 5 \times 10^{-2}$ was declared significant. Statistical calculations were implemented in Mathematica (Wolfram Research, Inc., Champaign, Ill.).

Results

One hundred two papers were identified. Forty-three were prospective studies with a parallel control group, and two reports used a historical control group; these two studies with historical control groups were combined with the 43 parallel group studies for analysis (10–54). The other papers could not be used, most frequently because they did not contain a clinical trial of a pretreatment drug, did not report pain scores or pain frequencies, or did not include a control group.

In these 45 studies the patient groups were generally small- to medium-sized; about one-half had less than 100 patients. The smallest study had 38 patients; the largest had nearly 600 patients. Recent papers appeared to be incorporating better methods of experimental design, but many papers did not specify important elements. Twenty of the 45 papers did not specify blinding of patients and investigators. Twenty-two papers either did not randomly allocate patients to study groups or did not specify the method of allocation; of those papers claiming to use random allocation, very few gave sufficient details to confirm the validity of the random allocation method. Both randomized and nonrandomized trials were combined for meta-analysis. Seven drugs had a sufficient number of studies for meta-analysis; these were atracurium, d-tubocurarine, gallamine, pancuronium, small self-taming doses of succinylcholine, diazepam, and lidocaine. Thus seven separate meta-analyses were performed.

As evidenced by the dates of publication of the 45 reports, the problem of postoperative myalgias is of continuing interest (Table 1); additional studies have been published on a recurring basis since the initial report in 1954 by Churchill-Davidson (21). Also, a wide variety of methods has been tried, including electrolytes (calcium and magnesium) and vitamin C. The dosage of the study drug in the 45 papers was not listed in a consistent fashion; it is sometimes described as a total dose and sometimes as a dose

<u>Table 1</u>. Studies by Year of Publication

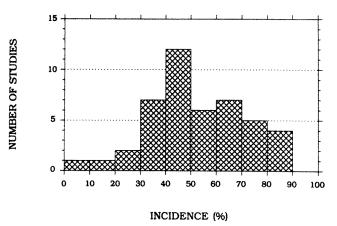
Year of publication	Articles published
1951–55	1
1956-60	3
1961–65	5
1 966 –70	4
1971–75	3
1976–80	8
1981–85	16
1986–89	5

per unit of body weight. In general, the published studies gave insufficient details about body weights to permit retrospective calculation of the dose per unit of body weight. Thus, even if a given study included several treatment groups given different doses of the study drug, all subjects receiving the same study drug were of necessity grouped for analysis. Some clinical reports included more than one study drug. In that instance, the results for each study drug were grouped into the appropriate meta-analyses.

The covariates that have been suggested by previous reports to modify the incidence of postoperative myalgias included postoperative ambulatory status, gender, age, interval between pretreatment and the administration of succinylcholine, and the dose of succinylcholine. Although at least one of these covariates were specified in most published papers, too much information was missing for covariate analysis to be attempted.

There was a much greater range of variability of the incidence in postoperative myalgias in the control groups of the 45 studies than might have been suspected. The incidence varied from as low as 5% to as high as 83% (Figure 1). The statistical analysis confirmed that there was a highly significant variability in treatment effect (Table 2); this was true in each of the seven pretreatment methods. A plot of the incidence of postoperative myalgias in the control groups versus the incidence of postoperative myalgias in the groups receiving the study drug also demonstrated this variability in treatment effect; this is shown for two of the study drugs, d-tubocurarine and succinylcholine self-taming (Figures 2 and 3). If the treatment effect were constant among studies, then all the data points would lie or group themselves along a straight line parallel to the line of identity. Instead, the data points are widely scattered.

Six of the seven pretreatments clearly reduced the incidence of postoperative myalgias by 22% (gallamine) to 38% (lidocaine) (Table 3). There was no difference in the size of the treatment effect of these six pretreatments ($\chi_5^2 = 3.56$; P = 0.61). Thus, the



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<u>Figure 1</u>. Histogram showing the distribution of the incidence of postoperative myalgia in the control group(s) in the 45 reports chosen for analysis.

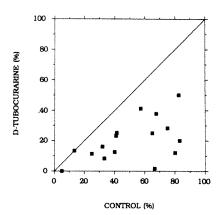
Table 2. Treatment Effect Consistency Among Studies

	Typical dose	No. of	No. of		n-study geneity
Drug	(mg)	studies	subjects	Test statistic	Probability
ATR	3	4	212	$\chi_3^2 = 8.80$	3.21×10^{-2}
DIA	10	8	974	$\chi_7^2 = 32.9$	2.80×10^{-5}
DTC	3	16	1604	$\chi_{15}^{2} = 138.1$	2.81×10^{-9}
GAL	10	12	1339	$\chi_{11}^2 = 65.6$	8.36×10^{-10}
LID	150	5	750	$\chi_4^2 = 22.5$	1.58×10^{-4}
PAN	1	6	355	$\chi_{\rm S}^2 = 20.7$	9.40×10^{-4}
SCH	10	7	407	$\chi_6^2 = 72.7$	8.50×10^{-14}

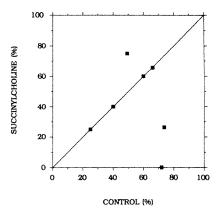
ATR, atracurium; DIA, diazepam; DTC, d-tubocurarine; GAL, gallamine; LID, lidocaine; PAN, pancuronium; SCH, succinylcholine self-taming. $\chi_{\rm df}^2$, homogeneity χ^2 statistic; df, degrees of freedom.

incidence of postoperative myalgias can be reduced by about three-tenths by three quite different drug groups. The treatment effect for succinylcholine self-taming had a very wide 95% confidence interval (-17% to 44%); statistically, it is very unlikely that succinylcholine in small self-taming doses significantly decreases the incidence of postoperative myalgias.

Treatment effects could also be evaluated by examination of the pain incidence comparison plots (Figures 2 and 3). In such a plot, points lying below the line of identity represent studies with an incidence of myalgias higher in the control group than in the treatment group; such studies favor the efficacy of the pretreatment drug. In the plot of *d*-tubocurarine (Figure 2), all points lie on or below the line of identity; plots for atracurium, diazepam, gallamine, lidocaine, and pancuronium are similar to that of *d*-tubocurarine. By contrast, in the succinylcholine self-taming plot (Figure 3) the points were more or



<u>Figure 2</u>. Scatter plot comparing the incidence of postoperative myalgia in the control and treatment group(s) for each of the 16 studies using *d*-tubocurarine.



<u>Figure 3</u>. Scatter plot comparing the incidence of postoperative myalgia in the control and treatment group(s) for each of the seven studies using succinylcholine self-taming.

less evenly distributed along and on both sides of the line.

Discussion

The literature concerning the prevention of succinylcholine-induced myalgias abounds with contradictions. The gold standard by which to resolve such inconsistencies would be a very large, multicenter, double-blind, randomized, placebo-controlled clinical trial that would simultaneously compare all the putative pretreatment drugs in a dose-response fashion; this trial would also be stratified by important covariates such as gender and ambulatory status. It is unlikely that such a clinical trial will ever be performed

Alternatively, one can attempt to synthesize the results of existing published reports. Such a literature review in a narrative style is commonly called a medical intelligence or review article and has an

Table 3. Treatment Efficacy

Drug	Reference	Risk difference (mean ± se)	Z-score test statistic	Probability
ATR	16, 35, 37, 44	0.32 ± 0.11	2.85	4.33×10^{-3}
DIA	20, 23, 25, 26, 34,	0.24 ± 0.08	3.12	1.83×10^{-3}
	39, 48, 49			
DTC	10-12, 20, 22, 24,	0.30 ± 0.06	5.01	5.46×10^{-7}
	26, 28, 33, 34, 36,			
	39, 44, 45, 52, 54			
GAL	10, 12, 15, 17, 21,	0.22 ± 0.06	3.85	1.16×10^{-4}
	28-30, 38, 41, 51, 52			
LID	18, 27, 32, 36, 47	0.38 ± 0.08	4.98	6.27×10^{-7}
PAN	10, 12, 14, 28, 38, 52	0.25 ± 0.08	3.00	2.70×10^{-3}
SCH	13, 22, 38, 43, 46,	0.14 ± 0.16	0.87	3.82×10^{-1}
	50, 53			

ATR, atracurium; DIA, diazepam; DTC, d-tubocurarine; GAL, gallamine; LID, lidocaine; PAN, pancuronium; SCH, succinykholine self-taming.

established role in medical journals. Less appreciated or explicitly discussed are the limitations of any literature review; these limitations include (a) sampling bias due to reporting and publication policies of medical journals; (b) the absence in published studies of specific data necessary for critical review; (c) biased exclusion of studies by the literature reviewer; (d) the uneven quality of the primary data; and (e) biased outcome interpretation (6).

Which studies are pooled together in a narrative review often seems quite subjective. For example, in 1962 Bryson and Ormston reported that "contrary to the experience of other authors . . ., the previous use of gallamine . . . does not reduce the incidence of muscle pains" (15). Later, in a 1975 narrative review Riding stated that "there is general agreement that small doses of non-depolarizing muscle relaxants, given before suxamethonium, lessen . . . the incidence of muscle pain" (55). Riding either did not consider or did not accept the report by Bryson et al. Was this an oversight, a prudent rejection, or a biased exclusion? No explicit standards for accumulating or discounting evidence were given. Current textbooks of anesthesia also reflect the difficulty of synthesizing an interpretation of these inconsistent published reports; authors of textbooks usually cite only a limited few of the 45 available studies.

Meta-analysis offers methods for literature review that constitute a structured alternative to the narrative summary; compared to a narrative review, meta-analysis systematically includes all studies and quantitatively amasses the data. An extensive body of published materials is now available to guide the investigator in attempting meta-analysis (2,5,6,56). Meta-analysis has its own set of experimental methods, which include (a) defining the problem and the criteria for admission of studies into meta-analysis;

(b) locating the clinical trials; (c) classifying and coding study characteristics; (d) quantitatively measuring study characteristics on a common scale; (e) aggregating study findings; and (f) reporting the results (6).

Some serious reservations have, however, been raised concerning meta-analysis. These include the suspicion that meta-analysis is really a "garbage in/garbage out" exercise camouflaged by fancy statistics and the fear that "good science" is being driven out by the weight of numbers of "bad science" (57). In addition, the best choice of statistical methods for meta-analysis under various conditions has not been fully explored (6). Statisticians also do not agree on the suitability of currently available methods. For example, the variance components method used for this report has been both supported (5) and criticized (58). Nevertheless, the preponderance of arguments favors the continued use of meta-analysis (2,5,6,57).

The meta-analyses performed for this report confirmed the ability of pretreatment with several nondepolarizing muscle relaxants, a benzodiazepine, and a local anesthetic to lower to a significant degree the incidence of muscle aches after succinylcholine administration, i.e., by about 30%. Succinylcholine in small self-taming doses was unsuccessful. The heterogeneity of treatment effect implied the importance of known (e.g., gender, ambulatory status) and unknown covariates in explaining the wide range of reported incidences of postoperative myalgias. The lack of detail in the 45 reports prevented an analysis of these covariates. Meta-analysis provided a reasonable answer to a clinical controversy by combining the results of existing research reports. Other clinical controversies in anesthesia may also be amenable to resolution through the use of meta-analysis.

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Single-Dose Interpleural Versus Intercostal Blockade: Nerve Block Characteristics and Plasma Concentration Profiles After Administration of 0.5% Bupivacaine With Epinephrine

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VAN KLEEF JW, BURM AGL, VLETTER AA. Single-dose interpleural versus intercostal blockade: nerve block characteristics and plasma concentration profiles after administration of 0.5% bupivacaine with epinephrine. Anesth Analg 1990;70:484–8.

Analgesic effects and plasma concentration profiles after interpleural (IP) or intercostal (IC) administration of 21 mL of 0.5% bupivacaine with epinephrine (5 μ g/mL) were studied in 24 patients (IP group: n=12; IC group: n=12) who had undergone cholecystectomy or renal surgery. The number of blocked dermatomes, as assessed by pinprick, was more variable between patients in the IP group (2–9 dermatomes) than in the IC group (6–8 dermatomes). The mean time intervals from the injection to two-dermatome regression and to first need for additional pain medication were 4 h (IP) and 5.5 h (IC) (P < 0.02) and 5.3 h (IP) and 9.8 h (IC) (P = 0.002), respectively. The degree of postoperative pain was evaluated by means of a visual analogue scale. This gradually increased during the first 4 h in the IP group (P < 0.001), but not in the IC group.

Peak bupivacaine concentrations in arterial plasma were approximately 10% higher than those in venous plasma and were attained more rapidly. Peak arterial plasma concentrations after IP injection (2.07 \pm 0.53 μ g/mL) were significantly higher (P < 0.005) than those after IC administration (1.36 ± 0.48 µg/mL). Peak venous plasma concentrations showed a similar difference (IP: 1.86 ± 0.45 $\mu g/mL$; IC: 1.21 ± 0.48 $\mu g/mL$; P < 0.005). Peak concentrations were attained later after IP injection both in arteria! (IP: 16.3 ± 4.6 min; IC: 8.8 ± 5.4 min; P <0.002) and venous plasma (IP: 20.0 \pm 7.1 min; IC 13.3 \pm 6.9 min; P < 0.05). This study demonstrates that singledose IP blocks provide shorter lasting postoperative pain relief than do IC blocks. In addition, plasma concentrations of bupivacaine are significantly higher after IP than after IC blocks.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interpleural, intercostal. ANESTHETICS, LOCAL—bupivacaine. PAIN, POSTOPERATIVE.

Relief of postoperative pain after upper abdominal surgery permits early ambulation and facilitates ventilation. Several methods are used to provide pain relief. Despite their side effects—including nausea, vomiting, and respiratory depression—systemic administration of opioids remains the most commonly used method to relieve postoperative pain. Epidural administration of local anesthetics or opioids, and intercostal (IC) blocks performed by multiple injections also have an established role in providing analgesia after upper abdominal or thoracic surgery,

but are applied less frequently (1). Interpleural (IP) administration of a local anesthetic has recently been reported to provide satisfactory pain relief after surgery with unilateral incisions. First described in 1986, the technique has rapidly captured the imagination of those responsible for the management of postoperative pain. Compared with multiple IC blocks, the technique has the advantage of requiring only a single needle puncture, and compared with continuous IC blocks it has the advantage of the relative simplicity of the technique (1,2). In addition, lack of sympathetic blockade, systemic hypotension, and respiratory depression are advantages of IP blockade compared with epidural blockade.

According to Rocco et al. (2), after IP injection "resulting local anesthetic blood levels appear to be appreciably lower than those associated with the administration of an equal dosage of local anesthetic for multiple IC nerve blocks." Kambam et al. (3)

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stated that the plasma concentrations of local anesthetics are three to four times lower after IP injection than after IC administration. However, controlled studies comparing the efficacy of IC and IP block and associated plasma concentrations are lacking.

The present study was designed to determine and compare plasma concentrations and analgesic effects of 0.5% bupivacaine with epinephrine (5 μ g/mL) after a single-dose IP or IC administration in patients having a cholecystectomy or renal surgery.

Methods

Twenty-four consenting adult patients, with ages ranging from 21 to 62 yr and ASA physical status I or II, were enrolled in this study. The study was approved by the institutional committee on medical ethics. Patients with a history of traumatic or spontaneous pneumothorax, hemothorax, pleuritis with or without fibrosis, and/or allergy to local anesthetics were excluded from the study. Contraindications also included local infection and bullous emphysema. Eighteen patients had a cholecystectomy (subcostal incision), and six patients had renal surgery (lumbotomy). The patients were classified randomly into one of two groups (12 patients in each group) and were given either an IP injection of 21 mL of 0.5% bupivacaine hydrochloride (105 mg) with epinephrine (5 μ g/mL) or seven IC injections of 3 mL of 0.5% bupivacaine hydrochloride (105 mg) with epinephrine $(5 \mu g/mL)$.

The patients received premedication with temazepam (20 mg) with an anesthetic induction with thiopental and succinylcholine for tracheal intubation. Anesthesia was maintained with 33% nitrous oxide in oxygen, fentanyl (0.1 mg every half-hour), pancuronium, and enflurane. Residual fentanyl effects were antagonized with 0.08 mg of naloxone in two patients in the IP group and in one patient in the IC group.

After induction of general anesthesia 20- and 16-gauge catheters were introduced into the radial artery and right jugular vein, respectively. After closure of the surgical incision but before extubation the patients were turned to the lateral decubitus position with the operated side uppermost and the sixth to 12th IC spaces were identified. In the IP group a 16-gauge Tuohy needle with a freely moving air-filled glass syringe was introduced approximately 10 cm from the midline into the eighth or ninth IC space just above the rib. The syringe and needle were slowly advanced until the pleural space was entered, as evidenced by the descent of the plunger of the

syringe. A clear nylon catheter (outside diameter 1.1 mm, length 900 mm) with three lateral eyes and a closed end was advanced 10 cm into the pleural space through the needle, which was then withdrawn. A bacterial filter (0.2 μ m) was fitted to the end of the catheter. Subsequently a test dose (3 mL of 0.5% bupivacaine with 15 μ g of epinephrine) was injected. Two minutes thereafter, in the absence of symptoms indicative of an intravascular injection, 18 mL of 0.5% bupivacaine with epinephrine (5 μ g/mL) was injected. In IC patients seven IC nerves were blocked, each with 3 mL of 0.5% bupivacaine with epinephrine (5 μ g/mL), using the IC block technique as described by Moore (4). Upon completion of the regional anesthetic procedure, patients were turned to the supine position and general anesthesia was terminated.

The quality of the resulting block was tested by pinprick every hour for 8 h. The degree of postoperative pain was evaluated by means of a visual analogue pain score scale (VAS 0–10 cm).

Arterial and central venous blood samples (5 mL) were collected before injection and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, and 120 min after the administration of bupivacaine. Additional central venous blood samples were collected at 180, 240, 300, 360, 420, and 480 min after the administration of bupivacaine. Plasma was obtained by centrifugation and stored at -20°C awaiting analysis. A gas chromatographic technique, described earlier (5), was used to determine the plasma concentrations of bupivacaine.

The data were assessed for normality using the Shapiro–Wilk test. Based on the outcome of this test, further statistical evaluation was done by the paired t-test or Wilcoxon paired sample test for intragroup comparisons and the two-sample t-test or Mann–Whitney U-test for intergroup comparisons. The Fisher exact test was used for comparison of proportions. Visual analogue pain scores in the IP and IC groups were evaluated by comparing the overall mean scores, obtained during the first 4 h, using the two-sample t-test and with linear regression analysis, followed by t-tests of the slopes. A P value of <0.05 was regarded as the minimum level of statistical significance.

Results

The patients in the IC and IP groups were similar with regard to age, weight, height, gender, ASA physical status, and duration of surgery (Table 1).

<u>Table 1</u>. Patient Characteristics and Duration of Surgery^a

	IP group	IC group	P
Age (yr)	41 ± 15	50 ± 8	NS
Weight (kg)	73 ± 10	76 ± 13	NS
Height (cm)	170 ± 5	170 ± 11	NS
Gender (male/female)	2/10	4/8	NS
ASA physical status (I/II)	9/3	8/4	NS
Duration of operation (min)	143 ± 43	145 ± 48	NS

IP group, patients receiving interpleural administration of bupivacaine with epinephrine; IC group, patients receiving intercostal administration of bupivacaine with epinephrine; NS, not significant.

Data are mean ± sp or proportions, as appropriate.

<u>Table 2</u>. Number of Blocked Dermatomes, Time to Two-Dermatome Regression of the Block, and Time Until the First Additional Pain Medication^a

	IP group	IC group	P
Number of blocked	6.5	7.0	NS
dermatomes	(2.0-9.0)	(6.0-8.0)	
Two-dermatome regression (h)	4.0	5.5	< 0.02
3	(2.0-5.0)	(3.0 to >8)	
Time till first additional pain	5.3	9.8	0.002
medication (h) ^b	(4.0-10.0)	(6.8-18.0)	

Abbreviations as in Table 1.

Data are medians and (between brackets) ranges.

The number of blocked dermatomes with the IP and IC blocks is summarized in Table 2. The median number of blocked dermatomes was similar after IP and IC administration, but the number of blocked dermatomes was more variable between patients in the IP group. Although in the IC group seven IC nerves were blocked, one patient experienced analgesia to pinprick in eight dermatomes (T-5 to T-12). The time until two-dermatome regression of the block was shorter after IP than after IC administration. Ten of 12 patients in each group needed additional pain medication within the first 24 h. The time until the first additional pain medication was shorter after IP than after IC administration. Visual analogue pain scores during the first 4 h are presented in Table 3. The overall mean VAS during the first 4 h was similar in the IP and the IC groups. However, VAS during the first 4 h showed a gradual increase in the IP group (P < 0.001) but not in the IC group. Visual analogue pain scores after 4 h are not reported, as 5 of 12 patients in the IP group received additional pain medication between 4 and 5 h after the injection.

Mean plasma concentrations as a function of time are shown in Figure 1. Pharmacokinetic data are presented in Table 4. Peak concentrations in arterial

<u>Table 3</u>. Visual Analogue Scale Ratings During the First 4 h^a

Time (h)	IP group	IC group
1	1.1 ± 1.2	1.5 ± 0.9
2	1.2 ± 1.1	1.5 ± 0.9
3	2.4 ± 1.4	1.7 ± 0.7
4	3.4 ± 2.6	1.8 ± 0.9

Abbreviations as in Table 1. Data are mean ± sp.

plasma were approximately 10% higher than those in venous plasma, but only after IP administration was the difference statistically significant. Peak concentrations were attained later in venous plasma than in arterial plasma, both after IP and IC administration. There were no significant differences in the areas under the arterial and venous plasma concentration curves within each group. Peak plasma concentrations were approximately 50% higher after IP than after IC administration. Also, peak concentrations were attained later after IP injection. Areas under the plasma concentration curves (AUCs) during the first 2 h were approximately 50% higher after IP than after IC administration. However, there was no significant difference in the AUCs determined over 8 h.

Discussion

Injection of a local anesthetic into the IP space has been reported to provide postoperative pain relief in patients after cholecystectomy, breast, or renal surgery, as well as in patients with multiple rib fractures. Analgesia with this technique is most likely due to retrograde diffusion of the drug through the parietal pleura causing IC nerve blocks (1,2). We compared the block characteristics of a single IP injection with those of multiple IC nerve blocks in patients who had undergone either a cholecystectomy (subcostal incision) or renal surgery (lumbotomy). The same amount of bupivacaine (105 mg) was injected interpleurally or intercostally. The study demonstrated that although the median number of blocked dermatomes, as determined by pinprick, was similar after IC and IP injection, the variation in the number of blocked segments was greater after IP injection. Also, IP block lasted for a shorter period of time than IC block. During the first 4 h VAS showed a gradual increase in the IP group, but not in the IC group. Although the duration of action of the IP block was shorter than the duration of IC block, this is a relative disadvantage. Once an IP catheter has been inserted, the duration of the block may be prolonged, of

^bNumber of patients receiving additional pain medication: n = 10 in both groups.

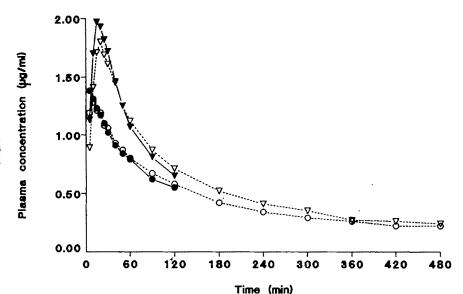


Figure 1. Mean arterial (closed symbols) and venous (open symbols) plasma concentrations of bupivacaine versus time after interpleural (triangles) and intercostal (circles) injection.

<u>Table 4</u>. Arterial and Venous Peak Plasma Concentrations, Peak Times, and Areas Under the Curve After Interpleural or Intercostal Administration of 21 mL 0.5% Bupivacaine With Epinephrine (5 µg/mL)^a

Parameter	Sampling site	IP group	IC group	P
C _{max} (µg/mL)	Arterial	2.07 ± 0.53	1.36 ± 0.48	< 0.005
	Venous	1.86 ± 0.45	1.21 ± 0.48	< 0.005
	P	< 0.001	NS	
t _{max} (min)	Arterial	16.3 ± 4.6	8.8 ± 5.4	< 0.002
	Venous	20.0 ± 7.1	13.3 ± 6.9	< 0.05
	P	< 0.02	< 0.05	
AUC (0-2 h)	Arterial	137 ± 41	92 ± 32	< 0.01
$(\mu g ml^{-1} min)$	Venous	135 ± 45	90 ± 33	< 0.02
,	P	NS	NS	
AUC (0-8 h)				
$(\mu g ml^{-1} min)$	Venous	272 ± 102	215 ± 63	NS

 C_{max} , arterial and venous peak plasma concentrations; t_{max} , peak times; AUC, areas under the curve. All other abbreviations as in Table 1.

*Data are mean \pm sp.

course, if the catheter is left in place by the repeated injection of local anesthetics or by continuous infusion.

Comparison of the concentration profiles after single IP injection and multiple IC injections shows that with the same dose, peak arterial plasma concentrations after IP injection (2.07 \pm 0.53 μ g/mL) are significantly higher than those after IC administration (1.36 \pm 0.48 μ g/mL). This contrasts with statements by Rocco et al. (2) and Kambam et al. (3) that blood concentrations are lower after IP than after IC administration. However, the statements of these authors are based on uncontrolled studies of the blood concentrations after IP administration only.

Our finding that IP injection of bupivacaine produces a unilateral block is consistent with the proposed mechanism that this block results from an action of the local anesthetic on IC nerves. However, blocking characteristics are clearly different with the two techniques. This may be related to differences in systemic drug absorption. More extensive absorption after IP injection results in higher peak plasma concentrations and will result in lower concentrations at the IC nerves, leading to less intensive blocking characteristics (6) and a shorter duration of action, as has been demonstrated in this study.

There are several reports of bupivacaine plasma concentrations after IP injection, some of them reporting venous concentrations (2,7-9), others reporting arterial concentrations (1,3,10–12). Despite these different sampling sites, peak plasma concentrations of bupivacaine were usually found 15-30 min after the injection. In those studies peak plasma concentrations varied from <0.5 μ g/mL to >2.0 μ g/mL. These differences cannot be explained by the injection of different doses in different studies. If peak plasma concentrations are normalized for a 100-mg dose, the same variability is obtained. A possible source of variations in plasma concentrations between studies is the blood sampling site (arterial versus venous). In the present study both arterial and central venous blood samples were collected. Mean peak concentrations in arterial plasma were approximately 10% higher than those in venous plasma, after both IP and IC administration. Although the differences reached statistical significance after IP administration, they were relatively small compared with the interindividual differences. Concentrations in ANESTH ANALG

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plasma obtained from samples taken from a peripheral vein may be lower than central venous concentrations, but we believe that the variability in measured bupivacaine concentrations between studies cannot be fully explained by differences in the blood sampling site.

Plasma concentrations measured after IP injection in this study (arterial $C_{max} = 2.07 \pm 0.53 \mu g/mg$, range 0.98-3.21 μ g/mL) were higher than those reported previously. A factor that was different in this study compared with most previous studies is the time at which the local anesthetic was injected. In the present study bupivacaine was administered after surgery was completed, but before removal of the tracheal tube, whereas in other studies injections were given in the recovery period. It is conceivable that changes in cardiac output and local perfusion associated with recovery from anesthesia and surgery affect the absorption and disposition of local anesthetic and, therefore, the plasma concentrations. In a study in which the local anesthetic was injected in the recovery period, Symreng et al. (11) found bupivacaine plasma concentrations of $0.44-1.50 \mu g/mL$, whereas in another study by the same investigators (12), in which the local anesthetic was injected during anesthesia, before surgery, the mean peak plasma concentration was 2.0 μ g/mL.

Plasma concentrations of bupivacaine that can cause convulsions in humans have been reported to be as low as 2.3 μ g/mL and as high as 4.0 μ g/mL (3). Although in this study peak arterial plasma concentrations of bupivacaine after IP injection exceeded 2 μ g/mL in 6 of 12 patients, and 3 μ g/mL in one patient, signs or symptoms of systemic toxicity were not observed in any patient. These high plasma concentrations indicate, however, that the margin of safety is small and that IP blockade should be used with caution. Further controlled studies of factors that may influence plasma concentrations, such as the timing of the injection of the local anesthetic, are warranted.

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Is Chronic Ethanol Consumption Associated With Tolerance to Intrathecal Lidocaine in the Rat?

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Intoxication with alcohols can produce anesthesia. In contrast, chronic ethanol consumption can produce tolerance to inhaled and other general anesthetics. We tested whether ongoing consumption decreased, and whether withdrawal from such consumption increased, the intrathecal dose of lidocaine that induces sensory and motor blockade in female Sprague—Dawley rats. Sensory blockade was assessed using the tail-flick test, and motor blockade by the animal's inability to move its hind limbs. Rats were tested before commencing ethanol intake; during ethanol ingestion (9 days after beginning ingestion); and on the 15th day of ingestion, 14 h after withdrawing ethanol from their diet. Pair-fed control rats were tested at the same intervals. Ongoing administration of ethanol decreased the dose of

lidocaine required to produce sensory blockade, but this difference was not significant relative to the control group (i.e., the difference was significant within group but not across groups). Withdrawal of ethanol increased the dose requirements for sensory and motor blockade by 80% and 53% (P < 0.01 and P < 0.001) and decreased the duration of the motor blockade (P < 0.01). Dose requirements producing sensory block differed between alcoholic and control groups (P < 0.001). These results suggest that chronic ethanol intake produces tolerance to the local anesthetic effects of lidocaine. Whether this change results from a change in kinetics or in sensitivity is not known, but the latter would seem more likely, because duration of blockade was minimally affected or unaffected.

Key Words: ANESTHETICS, LOCAL—effect of alcoholism. ALCOHOL, ALCOHOLISM—effect on local anesthetics.

Acute intoxication with ethanol decreases anesthetic requirement for barbiturates (1) and inhaled agents (2). In contrast, patients who are chronic alcoholics but are not immediately under the influence of alcohol may require more than the usual doses of anesthetics to obtain anesthesia (3–5). Withdrawal from chronic administration of alcohol increases MAC for isoflurane in mice (6).

We have extended these observations by examining the possibility that inebriation might decrease the dose of lidocaine required to produce spinal anesthesia. Similarly, we studied whether withdrawal from chronic administration of ethanol increased lidocaine dose requirements.

Methods

Anesthesia and Surgical Procedures

The study was approved by the Committee on Animal Research of the University of California, San Francisco. Anesthesia was induced in female Sprague–Dawley rats (225–300 g) by intraperitoneal administration of 60 mg/kg methohexital. Additional doses of 5–10 mg were given as required. Surgery was performed with the animal in a Kopf stereotaxic apparatus.

PE-10 polyethylene catheters (I.D. 0.28 mm and O.D. 0.61 mm) were cut to 15-cm lengths and placed intrathecally using the technique described by Yaksh (7). A 2–3-cm midline skin incision was made at the base of the skull, and the fascia and the superficial neck muscles were retracted to expose the atlanto-occipital membrane. A slit was made in the exposed membrane through which the polyethylene catheter was inserted and advanced 9 cm caudally to lie at the caudal portion of the lumbar enlargement of the spinal cord. The catheters were then fixed to the skull using screws and dental acrylic. The skin was closed,

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and the animals were allowed to recover for 5 days before the study began.

Experiments

During the recovery period, animals had free access to water and Purina Chow. On the sixth postoperative day, we injected incremental doses of 2% hyperbaric lidocaine to produce sensory and motor block. Hyperbaric lidocaine 2% was prepared by mixing 5% (0.5 mL) and 1.5% (3 mL) lidocaine solutions (Astra Pharmaceutical Products, Westboro, Mass.), each solution containing 7.5% dextrose. Animals were placed in a restraint, and, before injection, we tested the tail-flick reflex by placing the rat's tail over a slit through which a 150-W bulb provided a heat stimulus. The time to movement of the tail was recorded. The average of three responses was taken as the control value (baseline). The restraints were then placed such that the animals were in an upright position. An initial 0.3-mg (15 μ L) dose of lidocaine was injected intrathecally using calibrated PE-10 tubing attached to a 25 μ L Hamilton syringe, with flow of local anesthetic monitored by the movement of a small bubble placed in the tubing. After 5 min, the tail-flick reflex was tested with rats placed supine, and the time to movement was recorded. We then administered successive doses of 0.1 mg (5 μ L) (all doses administered with the rat upright) until we obtained no response to the stimulus, and recorded the total dose required. To avoid damage to the tail, lack of occurrence of the tail-flick by 7 s resulted in termination of the stimulus, and the 7-s interval was assigned as the latency response (cutoff time).

Additional 0.1-mg doses of lidocaine were given until bilateral motor blockade of the hind limbs was obtained. The total dose was recorded. Motor blockade was defined by the rat's failure to withdraw its hind limbs when pulled. We then moved the rat from the restraint to a box $80 \times 100 \times 20$ cm to monitor the rat for the time to complete recovery from paralysis. The time elapsed from onset of to recovery from motor blockade was recorded. When ambulatory, rats were again placed in the restraint, and the tail-flick test was administered to evaluate sensory blockade. The time to complete recovery from sensory blockade was defined by the time required to return to control values. At the end of each experiment the intrathecal catheters were flushed with 10 μ L of saline.

Starting on postoperative day 6, pair-fed rats received a liquid diet containing 7% ethanol and 30% water in Nutrament (The Drakett Products Co., Cin-

cinnati, Ohio) for 15 days. Each 100 mL of Nutrament contains 4.5 g protein, 14.6 g carbohydrate, 2.6 g fat, 70.4 mg sodium, and 165 mg potassium. Nutrament also contains vitamins and minerals, including vitamins A, C, E, B₆, B₁₂, folic acid, thiamine, niacin, biotin, pantothenic acid, calcium, iron, phosphorus, iodine, magnesium, zinc, and copper. Control rats received the volume of Nutrament consumed by their treated counterparts over the previous 24 h, but a calorically equal amount of sucrose was substituted for ethanol. The dose of lidocaine required to produce motor and sensory blockade, and the duration of each type of blockade, were determined on the ninth day of ethanol intake (the resulting data indicate the effect of intoxication) and 14 h after withdrawal of ethanol on day 15 (these data indicate the effect of tolerance to alcohol).

When experiments were completed, the animals were killed by administration of an overdose of sodium pentobarbital. The spinal cord and the intrathecal catheter were exposed, and the position and patency of the catheter were determined by injecting methylene blue. Leakage of the dye to the adjacent tissues caused us to exclude an animal's data from study.

Statistical Analysis

The dose of lidocaine required to produce sensory and motor blockade and the duration of blockade within each group were evaluated using a one-way analysis of variance for repeated measures. When a significant difference was found unpaired t-tests were used to compare dose of lidocaine requirements and the duration of blockade in ethanol-treated versus control rats before treatment, on treatment day 9, and 14 h after ethanol withdrawal on day 15. A value of P < 0.05 identified a significant difference.

Results

Forty rats having intrathecal catheters entered the study. Results obtained from 20 rats were not included in the study, except as noted later in this section. Rats were excluded during the course of the study because of neurologic deficits or other health problems (six rats), or because of cutting off the external part of the catheter (two rats). Data from six rats were discarded after injection of methylene blue dye as autopsy revealed loss of catheter integrity. Data obtained from three alcoholic and three control rats were segregated from the primary data (in the

Table 1. Intrathecal Lidocaine Requirements for Producing Sensory and Motor Blocks in Intoxicated and Sobered Rats

	Control group $(n = 10)$			Ethanol group $(n = 10)$		
	Before liquid diet	9 Days of liquid diet	15 Days of liquid diet	Before ethanol	9 Days of ethanol	14 Hours after ethanol discontinued
Sensory block (mg/kg)	1.15 ± 0.25	1.23 ± 0.23	1.13 ± 0.15*	1.22 ± 0.32	0.69 ± 0.13^{b}	$2.20 \pm 0.16^{a,c}$
Motor block (mg/kg)	2.98 ± 0.32	3.78 ± 0.40	3.88 ± 0.35	3.17 ± 0.28	2.70 ± 0.37	4.85 ± 0.44^{c}
Sensory block (min)	34.5 ± 2.2	37.0 ± 2.3	40.0 ± 1.8	39.5 ± 2.3	44.5 ± 4.6	35.5 ± 1.9
Motor block (min)	23.0 ± 2.3	23.0 ± 1.1	23.0 ± 1.5	27.0 ± 1.7	24.0 ± 1.2	19.5 ± 1.6^{c}

Values are mean ± sr.

remaining 20 rats), as these controls were not pairfed. Examination of the results for these segregated unpaired rats showed that they were similar to the results found in the remaining rats.

Continuing administration of ethanol decreased the dose of ethanol required to produce sensory (but not motor) blockade (Table 1). That is, the required dose after 9 days of ethanol administration was less than the control dose. Neither the dose requirement nor the duration of blockade differed significantly within the control group, nor were the ninth-day values for the control group different from those for the group continuing to receive ethanol. Fourteen hours after withdrawal of ethanol, the lidocaine dose requirement increased significantly above that preceding ethanol treatment for sensory and motor blockade. Ethanol-treated rats required greater doses of lidocaine for sensory but not for motor blockade than control rats.

Although comparisons of pair-fed control and alcoholic rats did not show a difference in dose requirements for motor blockade, if non-pair-fed controls were included, the difference became significant (i.e., tolerance to motor blockade was observed).

The duration of the motor (but not sensory) blockade decreased significantly within the ethanol-treated group after ethanol withdrawal. However, duration did not differ between the ethanol and control groups.

Discussion

We found that withdrawal from chronic administration of alcohol increased the dose needed for spinal anesthesia. The cause of this tolerance is unknown. We speculate that it may be secondary to an alteration in neuronal susceptibility to ethanol-induced membrane fluidization. Neuronal membranes from ethanol-tolerant animals resist this fluidizing effect of ethanol (8). Resistance may result from adaptive changes in the lipid composition of neuronal cell membranes, such as increases in cholesterol content (9,10). The structural order of erythrocyte membranes obtained from chronic alcoholic patients is increased (11) and ethanol-tolerant rats are resistant to inhibition of sodium influx by ethanol (12). Tolerance to membrane perturbation and to inhibition of sodium influx follow a common time-course (12).

We also found that ongoing administration of alcohol decreased the dose of lidocaine needed to produce spinal analgesia (sensory block). Changes in the structure of the lipid bilayer may influence the behavior of membrane proteins, such as receptors or channels. In view of ethanol's local anesthetic activity and the fact that the process of conduction block is initiated by an increase in sodium permeability produced by the opening of sodium channels, it is not surprising that ethanol affects the voltage-dependent sodium channels in synaptosomal membranes prepared from rat forebrains (13). As lidocaine exerts its effect by prolonging the inactivation of the sodium channel, cross tolerance to ethanol involving an alteration in sodium channel properties may explain the increased lidocaine dose requirements.

Thus, our results may be explained by changes in neuronal membranes, i.e., a change in pharmacodynamics. An alternative explanation is that chronic administration of ethanol may have altered the rate of elimination of local anesthetic from the spinal canal, i.e., pharmacokinetics. For example, chronic administration may have produced an increase in oxygen consumption of the spinal cord and, perforce, an increase in local blood flow. We have no direct evidence (e.g., measurement of the rate of change of concentration of lidocaine in cerebrospinal fluid) to support or refute this explanation. However, the indirect evidence that we collected does not support the explanation: a more rapid rate of removal should have, but did not, shorten the duration of sensory blockade, and it only slightly decreased the duration of motor blockade.

 $^{^{\}circ}P < 0.0001$ versus the control group (intergroup analysis).

 $^{^{}b}P < 0.05$ versus the pretreatment value (intragroup analysis).

^{*}P < 0.01 versus the pretreatment value (intragroup analysis).

Ethanol administration for 9 days (continued administration) appeared to decrease the dose of lidocaine required to produce sensory blockade (Table 1). Although this effect was seen in the ethanoltreated rats (each rat as its own control), it was not seen in a comparison of the ethanol-treated and control rats (no ethanol). That is, we are not certain that this constitutes a real effect. Perhaps the effect seen in the ethanol-treated rats resulted from a cerebral effect rather than from an effect on the spinal cord or nerves. However, an effect on the cord or nerves would be consistent with results of previous studies that suggest that ethanol affects the gating mechanism of the sodium channel and that the receptors involved in this action also bind tetracaine (14). Our failure to find a significant difference between control and alcoholic rats may have a simple explanation: the depressant effect of ethanol may have been offset by the development of tolerance to ethanol itself. Membrane tolerance to ethanol can develop quickly (15). An alternative explanation is that local anesthetic activity of ethanol is not sufficient to decrease significantly the dose of lidocaine required to produce sensory and motor blockade.

If our results apply to humans, patients who are acutely intoxicated may require smaller doses of local anesthetics intrathecally. Patients who chronically abuse alcohol but are not intoxicated may require larger doses. However, this extrapolation to humans does not consider the structural and electrophysiologic alterations associated with alcoholic peripheral neuropathy. If chronic ethanol consumption affects the requirements of local anesthetics in humans, such an effect may be manifest after tolerance has developed and while the integrity of nerve axons remains intact.

Until the present work it appeared that no one had presented evidence, or even suggested, that alcoholism might alter the requirement for *local* anesthetics. What might explain the absence of a report suggesting that alcoholism and withdrawal from ethanol ingestion produces a tolerance to local anesthetics in patients? First, there is no prior report that would rouse our suspicions. Second, we normally give a dose of local anesthetic that appreciably exceeds what is needed for spinal analgesia. This excess might hide the increased requirement. Third, although a shortening of the duration of anesthesia (and even failure to develop adequate analgesia) might occur in a

subset of alcoholic patients, the subset might be too small to rouse suspicion, particularly as most of our patients are not alcoholics. That is, the occasional sobered alcoholic patient who is tolerant to the effects of local anesthetics may be written off as a normal variant. In any event, the correctness of our hypothesis is amenable to confirmation or refutation in the clinical arena.

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Effect of Nifedipine on Morphine-Induced Analgesia

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CARTA F, BIANCHI M, ARGENTON S, CERVI D, MAROLLA G, TAMBURINI M, BREDA M, FANTONI A, PANERAI AE. Effect of nifedipine on morphine-induced analgesia. Anesth Analg 1990;70:493–8.

Experimental data show that opiates interfere with calcium influx in the cell and that some calcium-channel blockers are analgesic. We therefore studied the effect of the calcium-receptor blocker nifedipine on the analgesic effect of morphine in the rat, using tail-flick responses, and in humans, using measurements of the intensity of postoperative pain. In both the experimental animals and humans nifedipine

significantly (P < 0.001) increased the analgesic effect of morphine independently of any effect on the metabolism of morphine. Respiratory and cardiovascular functions were not significantly changed by nifedipine. The data indicate that Ca^{2+} is important in mediating the analgesic effects of opiates and suggest that calcium-receptor blockers might find a place in the treatment of pain.

Key Words: ANALGESICS, MORPHINE. PHARMACOLOGY, CALCIUM-CHANNEL BLOCKERS—nifedipine. PAIN, POSTOPERATIVE.

It has been shown in several experimental models that endogenous (e.g., dynorphin) (1) and exogenous (e.g., buprenorphine) (2) κ -opiate receptor agonists interact with the calcium channel and modulate neurotransmitter release (3). Although less specifically, endogenous (e.g., β -endorphin) (4) and exogenous (e.g., morphine) (4) agonists of the μ -opiate receptor also have an inhibitory effect on cellular calcium influx (3). The effect of the μ -receptor agonist is indirect and is secondary to a hyperpolarization due to an increased efflux of potassium, which decreases calcium influx (5). These observations suggest that the analgesic effects of endogenous and exogenous opiates might be increased by the concomitant administration of calcium-channel blockers, and that these drugs might themselves exert an analgesic effect. Consistent with this hypothesis, it has been shown in experimental animals that ethylenediamine tetraacetic acid and ethyleneglycol-bis (β -aminoethylether)-N,N'-tetraacetic acid, two Ca2+ chelators, and

several blockers of the calcium channel increase both morphine-induced analgesia and pain thresholds when administered alone (6–8).

The present study was designed to verify whether the effect of calcium-channel blockers on morphine analgesia could be reproduced in humans. We chose the dihydropiridine calcium-channel blocker nifedipine because it is readily available in our hospitals and is formulated in a long-acting preparation. The effectiveness of the drug on morphine-induced analgesia was preliminarily tested in experimental animals, and, once effectiveness was confirmed, nifedipine was tested on postoperative pain in patients. Finally, morphine plasma concentrations were measured in placebo- or nifedipine-pretreated patients to evaluate any possible effect of the calcium-channel blocker on blood levels of the opiate.

Methods

Studies in Rats

Eight Sprague–Dawley CD rats, 150–180 g body wt (Charles River, Calco, Italy), housed with a 10- to 14-h dark/light cycle at $22 \pm 2^{\circ}$ C were used in each experimental group—i.e., 2.0 mg/kg nifedipine intraperitoneally, 1.25 mg/kg morphine intraperitoneally, and both drugs concomitantly. A saline-injected

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Table 1. Demographic Data for Patients

Pretreatment	n	Weight range (kg)	Weight (kg)"	Age range (yr)	Age (yr) ^a
Hysterectomy	***************************************				
Placebo	8	54-96	65.3 ± 14.5	38–56	43.5 ± 6.0
Nifedipine	8	54-90	67.3 ± 11.9	45-60	51.1 ± 6.5
Orthopedic surgery					
Placebo	5	58-70	65.2 ± 4.5	18-23	20.8 ± 1.9
Nifedipine	5	60–75	66.0 ± 6.3	22–53	29.8 ± 13.0

"Mean ± sp.

group was not used because we and others have repeatedly reported the complete absence of any detectable placebo effect under these experimental conditions. Analgesic responses were evaluated by the tail-flick method with procedures previously described in detail (9). The results were calculated as a percentage of the maximal possible effect (% MPE), according to the equation $[(TL - BL)/(ML - BL)] \times$ 100, where BL is the mean basal latency (3.5-4.0 s), TL is the test latency measured after treatments, and ML is the maximal latency accepted (8 s), chosen to avoid tissue damage to the tail. Analgesia was measured before and 15, 30, 45, and 60 min after treatment. In rats in which both nifedipine and morphine were injected, the nifedipine was administered intraperitoneally at the dose of 2.0 mg/kg immediately before the administration of a dose of morphine (1.25) mg/kg intraperitoneally), a dose that, in our hands, approximates the ED_{50} for morphine analgesia (10).

Statistical differences were evaluated by Kruskal–Wallis analysis of variance.

Studies in Humans

The experimental protocol was submitted to the ethical committee of the S. Carlo Borromeo Hospital, which approved the study; in Italy, however, acute studies do not need to be reviewed and approved by a review board for research in patients. Sixteen women, ASA physical status I or II, undergoing abdominal hysterectomies and 10 men undergoing orthopedic surgery entered the study after informed consent had been obtained. Demographic data for the patients are summarized in Table 1. The study was organized in a double-blind, placebo-controlled experimental design, in which each patient was assigned to the treatment group by balanced randomization to obtain the same number of patients in each treatment. Randomization was applied separately to the hysterectomy or orthopedic patients. Treatments included slow-release 20-mg tablets of nifedipine (Hoechst, Milan, Italy) or an identical placebo. The half-life of slow-release nifedipine is 15.2 ± 4.3 h compared with 3.9 ± 2.3 h with standard nifedipine tablets (11).

Treatments were administered at 2 PM and 11 PM on the day preceding surgery and at 7 AM the next morning, i.e., 60–90 min before the beginning of surgery. At the end of surgery, patients were transferred to the recovery room, and, within 10–20 min of the end of surgery, morphine (5.0 mg in slow infusion, i.e., half of the dose commonly used for management of postoperative pain) was administered to conscious patients with a Scott–Huskisson visual analogue scale (VAS) (12) score of 6 or more. The protocol allowed the administration of a second dose of the opiate if the patient complained of insufficient analgesia, but this was never the case.

Anesthetic management was kept constant in all patients: 10 mg of diazepam, 10 mg of the H_1 -blocker chlorpheniramine, and 0.5 mg of atropine were administered as preanesthetic medications; induction was with 5 mg/kg of thiopental, followed by 1 mg/kg of succinylcholine for tracheal intubation; anesthesia was maintained with 1% isofluorane, nitrous oxide in oxygen (70%/30%), and pancuronium with controlled ventilation.

Analgesia was evaluated by the patient using the VAS at the moment of awakening and 30, 60, 120, and 180 min after morphine administration. This VAS is a 10-cm horizontal line that the patient uses to evaluate the degree of pain. The left end of the line represents no pain, and the right end of the line is the maximum pain the patient can imagine. At the same time intervals after administration of morphine, the patient was asked to describe his or her pain as a numeric/verbal scale: "same as before" = 1, "less than before" = 2, "much less than before" = 3, and "no more pain" = 4. At the end of the observation period (180 min), the clinician gave an overall evaluation of the efficacy of analgesic treatment and gen-

eral conditions of the patient according to a 1-4 graded score: 1 = "no effect," 2 = "little effect," 3 = "good effect," 4 = "very good effect."

Before morphine administration—i.e., 10-20 min after the end of surgery, when the patients wake up—and thereafter at the same time intervals as pain was measured, the following were measured in all patients: heart rate, respiratory frequency, and systolic and diastolic blood pressures. Blood pressure was also measured before and after treatment with nifedipine or placebo. Pao₂, Paco₂, and pH were measured once, 60 min after the administration of the

Visual analogue scale values were expressed for statistical analysis as percentage of values before morphine administration to normalize values (baseline values were 7.6 \pm 0.9 and 7.1 \pm 1.4 [mean \pm sp] in gynecologic and orthopedic pain, respectively). Statistical analysis of results was obtained by the Kruskal-Wallis analysis of variance for percentages and score values, and analysis of variance followed by Dunnet or Student's t-test was used for multiple or single comparisons, respectively.

Morphine Plasma Concentrations

In the hysterectomy group, blood samples were obtained 30 and 60 min after morphine administration for measurement of plasma concentrations of the opiate in placebo- and nifedipine-pretreated patients. Morphine was measured by high-performance liquid chromatography using a method previously described in detail and validated, one that measures only unconjugated morphine (free morphine) (13). Differences in morphine plasma concentrations were evaluated by the Student's *t*-test.

Results

Studies in Rats

The analgesic effect of morphine was significantly increased 15 and 30 min after administration of the opiate in rats pretreated with the calcium-channel blocker nifedipine (Figure 1).

Studies in Humans

Pretreatment with nifedipine significantly increased the analgesic effect of morphine in both experimental

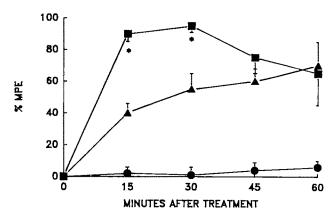


Figure 1. Analgesic thresholds in rats treated with 2 mg/kg of nifedipine intraperitoneally (♠); 1.25 mg/kg of morphine (♠); or the combination of the two drugs (♠). % MPE is described in text. $^*P < 0.01$ vs morphine alone.

groups, although it did not show any analgesic effect by itself (mean \pm sp VAS values before nifedipine = 7.8 ± 1.0 vs VAS values after nifedipine = 7.7 ± 0.7). Table 2 shows the percentage changes in VAS and in patients' evaluation scores of pain in the two experimental models. It is clear that the percentage decrease in pain is greater 60 and 120 min after the administration of morphine to nifedipine-pretreated patients than in placebo-pretreated patients in both experimental groups. Table 3 shows that the postoperative pain scores given by patients were significantly better 60, 120, and 180 min after morphine both in hysterectomy and orthopedic patients. Table 4 shows the values of the overall evaluation of the two treatments given by the blinded observer. Values for placebo pretreatment were always significantly lower than those associated with nifedipine pretreatment. The duration of anesthesia was 112 ± 28 min and 96 \pm 23 min (mean \pm sp) in women treated with nifedipine or placebo, respectively, and 135 ± 63 min and 153 ± 50 min (mean \pm sp) in men treated with nifedipine or placebo, respectively.

Figure 2 shows the data for mean Pao₂, Paco₂, pH, heart rate, respiratory frequency, and diastolic and systolic blood pressures in patients having hysterectomies. Nifedipine pretreatment did not affect any of the variables in these patients with the exception of a significant decrease in systolic pressure below baseline levels 60 and 90 min after the beginning of surgery; nifedipine had no effect on blood pressure in the period preceding surgery. Results obtained in hysterectomy patients duplicated those in men having orthopedic surgery (data not presented).

Morphine plasma concentrations were not significantly different in placebo- and nifedipine-pretreated

<u>Table 2</u>. Visual Analogue Scale Score as a Percentage of Visual Analogue Scale Scores Before Administration, at Different Times After Morphine Administration in Patients Pretreated With Placebo or Nifedipine

Pretreatment	Minutes after morphine				
	30	60	120	180	
Hysterectomy					
Placebo	86.5 ± 21.3	79.1 ± 16.1	81.3 ± 10.3	81.1 ± 7.9	
Nifedipine	73.9 ± 2.7	60.9 ± 9.9°	$61.3 \pm 12.1^{\circ}$	64.6 ± 15.3	
Orthopedic surgery					
Placebo	28.5 ± 4.3	35.3 ± 8.1	40.4 ± 11.2	23.1 ± 6.8	
Nifedipine	18.8 ± 2.2	24.2 ± 2.4^{a}	$22.2 \pm 4.2^{\circ}$	5.4 ± 4.2	

Values are mean \pm sp. $^{\circ}P < 0.001$ vs placebo.

<u>Table 3</u>. Patient Evaluation of Pain Relief at Different Times After Morphine Administration in Placebo or Nifedipine

Pretreatment	Minutes after morphine			
	30	60	120	180
Hysterectomy				
Placebo	1.4 ± 0.3	1.6 ± 0.4	1.4 ± 0.5	1.5 ± 0.6
Nifedipine	2.0 ± 0.5	2.4 ± 0.3^{e}	$2.6 \pm 0.4^{\circ}$	$2.4 \pm 0.2^{\circ}$
Orthopedic surgery				
Placebo	1.4 ± 0.2	1.9 ± 0.3	1.8 ± 0.4	1.6 ± 0.2
Nifedipine	2.2 ± 0.2^{s}	2.7 ± 0.4^{e}	$2.9 \pm 0.2^{\circ}$	2.2 ± 0.2

Values are mean \pm sp. *P < 0.001 vs placebo.

<u>Table 4</u>. Clinician Overall Evaluation of Treatment Efficacy

Surgery	Placebo	Nifedipine
Gynecologic	1.75 ± 0.4	$2.6 \pm 0.5^{\circ}$
Orthopedic	2.20 ± 0.4	3.0 ± 0.2^{a}

Values are mean \pm sp. "P < 0.001 vs placebo.

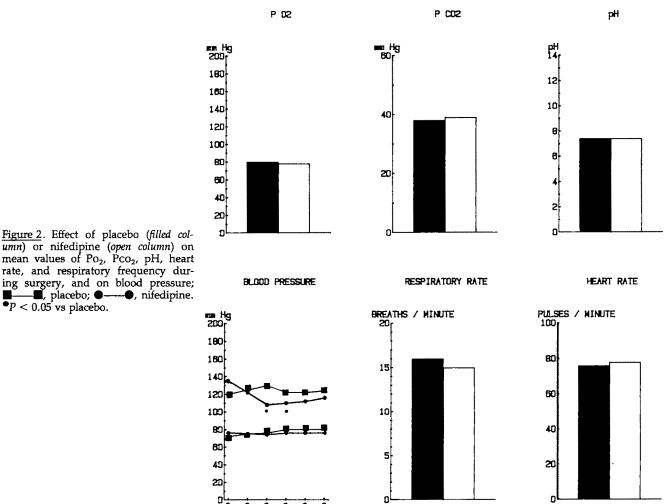
patients 30 min (plasma morphine = 16.0 ± 4.5 ng/mL vs 17.0 ± 5.4 ng/mL in placebo- and nifedipine-treated subjects, respectively) and 60 min (plasma morphine = 11.0 ± 5.0 ng/mL vs 9.0 ± 4.1 ng/mL in placebo- and nifedipine-treated subjects, respectively) after the administration of the opiate.

Discussion

The results presented confirm, in a model of acute pain in humans, the results on morphine analgesia obtained in experimental animals in this and previous studies (6–8). One straightforward explanation of the results is a decrease by nifedipine of morphine glucurono-conjugation in the liver, thus increasing levels

of free morphine. Free morphine is, of course, considered the most biologically active fraction of the opiate (14). However, our data exclude this possibility, as plasma concentrations of the unconjugated opiate were similar in placebo- or nifedipine-pretreated patients. Therefore, it remains undefined what pharmacologic basis underlies the effect of calcium blockers on morphine analgesia. Calciumchannel blockers might contribute to diminished influx of Ca²⁺ into the cell induced by morphine. It has been shown, in fact, in the myenteric plexus that agonists of μ -opiate receptor (which is what morphine is) increase potassium efflux thus decreasing calcium influx into the cell (5). An alternative explanation is that as κ -opiate receptor agonists directly decrease calcium influx in the cell (3) and behave as calcium blockers, nifedipine itself might exert an analgesic effect. Data supporting an analgesic effect of nifedipine have been reported in experimental animals, but for ethical reasons we could not test this possibility in our experimental setting.

During our study we did not encounter any unexpected side effects. The only statistically significant change was a slight decrease in systolic blood pressure in nifedipine-treated patients during surgery,



umn) or nifedipine (open column) on mean values of Po2, Pco2, pH, heart rate, and respiratory frequency during surgery, and on blood pressure;

, placebo; , nifedipine. $^{ullet}P < 0.05 \text{ vs placebo.}$

but this was probably related to anesthesia itself because it was minor in degree and brief in duration. Patients in all groups, irrespective of pretreatment with nifedipine or placebo, experienced nausea and vomiting.

HINUTES

In conclusion, the data presented suggest that pretreatment with nifedipine might turn out to be a useful procedure in ameliorating postoperative pain management when the use of opiates is foreseen. Studies are under way to explore whether pretreatment with nifedipine could be advantageous also during anesthetic procedures, e.g., during neuroleptoanesthesia, in which opiates are used as the only analgesic treatment.

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Inotropic Effect of Meperidine: Influence of Receptor and Ion Channel Blockers in the Rat Atrium

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Meperidine increases developed force in isolated rat atria. We initiated this study to determine if this positive inotropic effect was attenuated by commonly used receptor- and ion channel blockers. Neither naloxone (opioid blocker), phentolamine (α -adrenoceptor blocker), propranolol (β -adrenoceptor blocker), polaramine (H_1 -receptor blocker), ranitidine (H_2 -receptor blocker), verapamil (calciumchannel blocker), nor lidocaine (fast sodium-channel blocker) attenuated the positive inotropic effect of meperidine. However, after lidocaine pretreatment meperidine

increased contractile force by 57% (27%–80%) (median and 95% confidence interval), which is significantly more (P < 0.001) than the 21% (13%–35%) increase seen after pretreatment with saline. After Na,K-pump inhibition by ouabain, meperidine caused no further increase in contractility, but the atria still responded to isoproterenol with an increase in developed force. Conversely, meperidine prevented the positive inotropic effect of ouabain. These findings suggest that the positive inotropic effect of meperidine is mediated by an increase in intracellular sodium activity and not by regulation of the slow inward calcium channel.

Key Words: ANALGESICS, MEPERIDINE. HEART, CONTRACTILITY—meperidine.

Meperidine, a commonly used analgetic, has significant effects on the cardiovascular system. Its hemodynamic effects have been related to effects on the vasomotoric center (1), to release of histamine into the circulation (2–5), and to a direct effect on the myocardium (6–9). In the most recent studies on isolated ventricular (8) and atrial (9) muscle, a positive inotropic response was consistently demonstrated. The mechanism for this rise in cardiac contractility caused by meperidine was not examined. Therefore, the purpose of the present study was to try to elucidate this mechanism.

To examine if the positive inotropic effect of meperidine involves specific sarcolemmal receptors or, alternatively, regulation of specific ionic channels, we examined the effects of meperidine on isometric force in isolated left rat atria after blockade of opiate-, α -, and β -adrenergic-receptors, after blockade of histamine H_1 - and H_2 -receptors, and after partial blockade of slow inward calcium and fast sodium channels. Because only lidocaine interfered significantly with the inotropic effect of meperidine, we examined more specifically the interaction between meperidine and ouabain, which enhances contractility by increasing intracellular sodium activity.

Methods

Experimental Model

Sixty-six albino Wistar rats of either sex, weighing 210 g (208–230 g) (median and 95% confidence interval), were anesthetized by injecting 50 mg/kg pentobarbital into the peritoneal cavity. The heart was quickly dissected free and transferred into an ice-cold modified Ringer's solution. The left atrium was isolated during immersion and subsequently suspended in a bath (Figure 1, left panel).

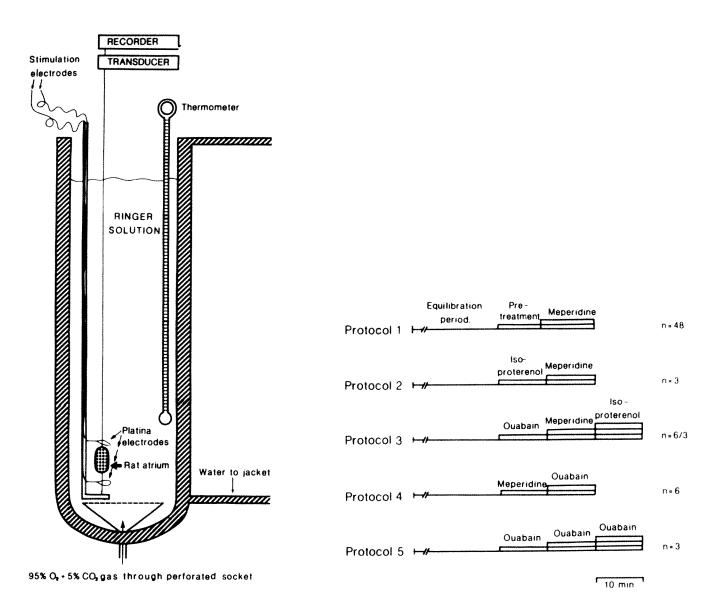
A water jacket kept temperature in the organ bath at 31.0°–31.8°C during the experiment. The organ bath was changed three times during the 60-min

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<u>Figure 1</u>. Left side shows a schematic drawing of the experimental equipment. The left atrium is fastened at one end in the bath; the other end is connected by a string to a force transducer. The five protocols are outlined to the right.

equilibration period. The chamber was filled with 20 mL of modified Ringer's solution with the following composition (ions in mmol/L); sodium 143.4, potassium 5.3, calcium 2.0, magnesium 1.1, chloride 126.4, dihydrogen phosphate 2.4, bicarbonate 25.0, and sulfate 1.1. The solution also contained 10.0 mmol/L glucose and was continuously bubbled with 95% O₂–5% CO₂, which was administered through the bottom of the chamber. The pH was 7.4.

Contractile force (F) and its first derivative with time (dF/dt) were monitored by a Grass Force Displacement Transducer (type FT03) and a carrier preamplifier and recorded on a four-channel Sand-

born recorder (model 7708A). The output from a passive derivating network was amplified by a DC-coupling Sandborn amplifier (model 760-1300).

The atria were stretched to a preload of 600 mg, then stimulated by bipolar platinum electrodes in the bath, with square-wave pulses of 2-ms duration at 1 Hz. The current was 20% above the threshold for stimulation in each experiment (range 5–20 mA).

The safeguards we took to avoid hypoxia in our atrial preparation were (a) we kept O_2 partial pressure in the bath close to 100% (95% O_2 –5% CO_2); (b) we lowered the temperature to 31° – 32° C; and (c) we used the left atrium, which can be paced at a lower rate (1 Hz) than the right atrium. The right atrium maintains its spontaneous heart rate of approximately 3 Hz. By pacing the left atrium at 1 Hz we reduced the oxygen demand of the atrium.

Cohen et al. (10) demonstrated in the right rat atrium (spontaneously beating at 2–3 Hz and kept at 30°C) that protein synthesis and adenosine triphosphate content did not increase when oxygen availability was facilitated by increasing the pressure above 1 atm. This was a strong indication of no oxygen deficit in their preparation exposed to a pressure of 1 atm. Because we also used the atrial preparation exposed to a pressure of 1 atm, but paced it at only 1 Hz, hypoxia is unlikely. An indication of satisfactory oxygenation of our preparation is that the preparation was stable for hours, and that no progressive deterioration followed meperidine administration, when oxygen consumption was obviously increased.

Experimental Procedure

Five different protocols were used (Figure 1; right panel).

Protocol 1. There were eight subgroups in this protocol. Atria from six rats were used in each subgroup. In random order one of the following eight solutions was added to the bath after baseline recordings:

- (a) modified Ringer's solution (1 mL)
- (b) naloxone, 10⁻⁴ M (opiate receptor blocker)
- (c) phentolamine, 10^{-5} M (α -adrenergic receptor blocker)
- (d) propranolol, 5×10^{-6} M (β -adrenergic receptor blocker)
- (e) polaramine, 10^{-5} M (histamine H_1 -receptor blocker)
- (f) ranitidine, 10^{-6} M (histamine H_2 -receptor blocker)
- (g) verapamil, 5×10^{-6} M (calcium channel blocker)
- (h) lidocaine, 5×10^{-5} M (fast sodium channel blocker)

The effects of these pretreatments were recorded at stable conditions 10 min after their application. Subsequently, 5×10^{-5} M meperidine was added to each of the subgroups, and the effects were recorded at stable conditions 10 min later.

There were no statistically significant differences among baseline values of F max, dF/dt max, dF/dt min, and rat weight in the eight subgroups. Pooled values were 550 mg (488–638 mg), 16 g/s (14–18 g/s), 11 g/s (10–12 g/s), and 220 g (207–233 g), respectively.

Protocol 2. It was of importance to determine whether an increase in contractility of approximately 20% modified the response to meperidine, because

F max increased after pretreatment in two of the subgroups in protocol 1 (naloxone and polaramine). In three preparations, therefore, 5×10^{-9} M isoproterenol, which increased contractility by about 25%, was administered before 5×10^{-5} M meperidine was added to the bath.

Protocol 3. Because an increase in intracellular Na $^+$ activity increases contractility, six preparations were pretreated with 2 \times 10 $^{-4}$ M ouabain before 5 \times 10 $^{-5}$ M meperidine was added. In three of the experiments, 5 \times 10 $^{-8}$ M isoproterenol (high dose) was subsequently added to determine the capacity of the preparation to respond with a further increase in force.

Protocol 4. The increase in developed force with meperidine was abolished after pretreatment with ouabain. In this protocol the effect of 10^{-4} M ouabain was therefore examined in three preparations after pretreatment with 10^{-4} M meperidine.

Protocol 5. A dose-response curve for determining the optimal ouabain concentration for force development was performed in three preparations examining the following doses: 5×10^{-6} , 10^{-5} , 5×10^{-5} , 10^{-4} , 5×10^{-4} , and 10^{-3} M.

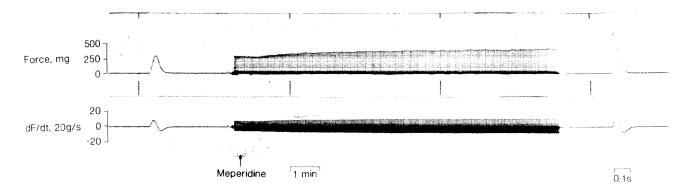
Preparation and Storage of Drugs

All drugs except propranolol and ranitidine were prepared from their salts 1 h before they were used. A 1 M propranolol solution was stored at -20° C protected from light and a 10^{-3} M solution was stored at 4° C (and protected from light); neither was stored longer than 1 wk.

Ranitidine was stored protected from light in the original ampules, containing 10 mg/mL ranitidine dissolved in distilled water. Ranitidine was delivered from Nycomed (Oslo, Norway) and lidocaine hydrochloride monohydrate from Astra (Södertälje, Sweden). Naloxone hydrochloride was a generous gift from Du Pont (Glenolden Laboratory, Glenolden, Pa.).

Statistical Analysis

Both the effect of blockers and the effect of meperidine after blockade were calculated as the percent change of baseline values of force and as dF/dt before blockers or placebo were administered. Therefore, assessment of the inotropic effect after meperidine



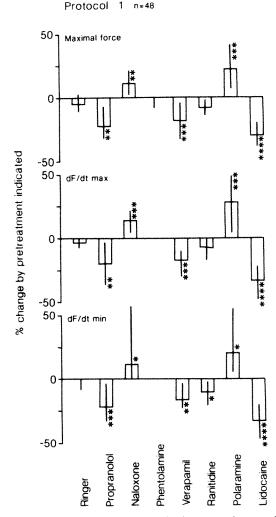
<u>Figure 2</u>. Tracing showing effects of meperidine on developed force and its derivative (dF/dt). Note the slight depression in force and maximum positive dF/dt preceding the increase seen during the subsequent 5–10 min until a steady-state condition is established

was not dependent on the inotropic effect of previous drug intervention. Data are presented as the median and as a nonparametric 95% confidence interval (in parentheses), based on Walsh numbers. The Kruskal–Wallis test with a multiple comparison procedure (11) was used to calculate two-tailed probability values of differences among the groups. P < 0.05 was considered statistically significant. The ouabain data (protocol 3, n = 6) were analyzed together with the blockers in protocol 1.

Results

The effects of meperidine on developed force and its first derivative in one experiment are shown in Figure 2. A similar response was observed in all experiments. A progressive increase in developed force started about 25–30 s after application of meperidine to the bath and was preceded by a slight decline that averaged 5% (2%–8%), and persisted for only about 15 s. About 5–7 min after having added meperidine to the bath, a stable elevated level of developed force was reached, 21% (13%–35%) above baseline. The maximal positive and maximal negative values of the first derivative of the developed force increased in parallel to the rise in developed force and stabilized at 19% (11%–26%) and 24% (10%–33%) above baseline, respectively.

The effects of the pretreatment in each subgroup in protocol 1 on developed force, dF/dt max, and dF/dt min, are presented in Figure 3. Contractility increased after naloxone and polaramine, decreased after propranolol, verapamil, and lidocaine, and remained unchanged after phentolamine and ranitidine—although dF/dt min was decreased by raniti-



<u>Figure 3</u>. Effects of pretreatments in the first part of protocol 1 on atrial function. The *bars* show median percent change and 95% confidence interval of maximal force (F), and the maximal positive derivative of F (i.e., dF/dt max), and the maximal negative derivative of F (i.e., dF/dt min). n indicates number of experiments. Number of asterisks indicates the level of significance compared to control (Ringer's). *P < 0.05, **P < 0.01, ***P < 0.001, ***P < 0.001

dine. As shown in Figure 4, the positive inotropic effect of meperidine was significantly altered by pretreatment with neither α -, β -, H_1 -, H_2 -, and opiate

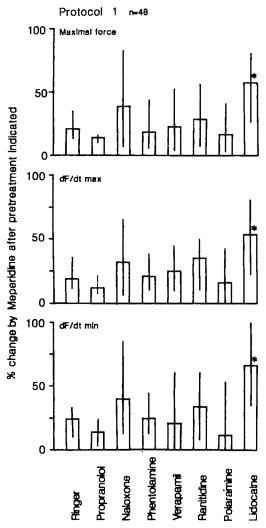
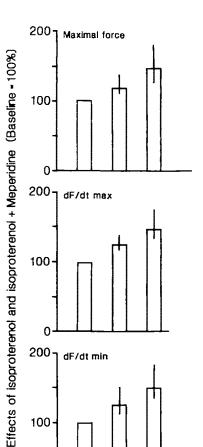


Figure 4. Effects of meperidine on atrial function after pretreatment with the agents indicated. Note that the increase in maximal force, dF/dt max, and dF/dt min associated with meperidine was potentiated only after lidocaine pretreatment. *P < 0.05 compared with the effect of meperidine after control (Ringer's). Symbols as in

receptor blockers, nor by Ca²⁺-blocker pretreatment. However, the inotropic response to meperidine increased after pretreatment by the fast sodiumchannel blocker lidocaine. Maximal development force increased by 57% (27%-80%), dF/dt max by 54% (22%–81%), and dF/dt min by 67% (34%–100%).

Protocol 2 demonstrates that the positive inotropic effect of meperidine was not inhibited by a moderate elevation of contractility induced by β -adrenoceptor stimulation (Figure 5). Isoproterenol increased maximal developed force, dF/dt max, and dF/dt min by 19% (10%-38%), 24% (17%-38%), and 25% (11%-50%), respectively. Subsequently administered meperidine increased the same parameters by an additional 24% (15%-31%), 19% (14%-27%), and 23% (17%–33%), respectively.



Protocol 2

Figure 5. Protocol 2. Effects of isoproterenol 5×10^{-9} M and the additional effects of meperidine on maximal force, dF/dt max, and dF/dt min.

Isoproterenol

Isoproterenol

Weperidine

100

In protocol 3 the positive inotropic effect of meperidine was blocked when the atria were pretreated with 2×10^{-4} M ouabain (Figure 6). In fact, F, dF/dt max, and dF/dt min fell by 5% (3%–10%) (P < 0.02), 12% (9%–18%) (P < 0.05), and 18% (12%–28%) (P <0.05), respectively, when meperidine was added.

The last part of protocol 3 (Figure 7) shows that after ouabain and additional meperidine pretreatments, isoproterenol still was able to increase F, dF/dt max, and dF/dt min substantially by 98% (4%-156%), 94% (0%-185%), and 92% (0%-160%), respectively. Note that the dose of isoproterenol was 10 times higher in protocol 3 than in protocol 2.

In protocol 4 we found that pretreatment with a high dose of meperidine (10⁻⁴ M) blocked the posi-

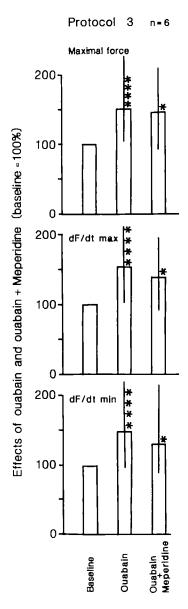


Figure 6. Protocol 3. Effects of ouabain and subsequent effect of meperidine on maximal force, dF/dt max, and dF/dt min. The number of asterisks indicates the level of significance compared with control (Ringer's). Symbols as in Figure 3.

tive inotropic effect of 10⁻⁴ M ouabain (Figure 8). When ouabain was added after meperidine, maximal force, dF/dt max, and dF/dt min decreased by 22% (13%–25%), 25% (17%–33%), and 25% (15%–29%), respectively.

In protocol 5 ouabain exerted a progressive rise in contractility when 5×10^{-6} to 5×10^{-4} M was added to the bath. No biphasic response was seen. These results agree with those presented by Akera et al. (12), who also used paced left rat atria and examined the dose-response curve for ouabain between 10^{-7} and 10⁻⁴ M. At an ouabain concentration of 10⁻³ M

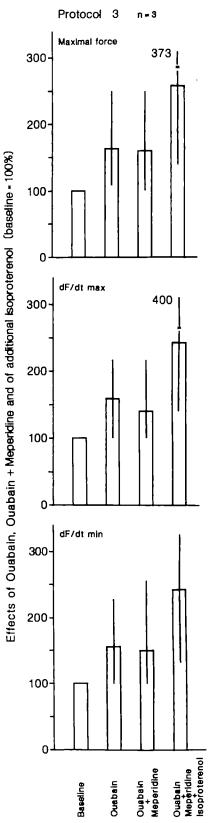
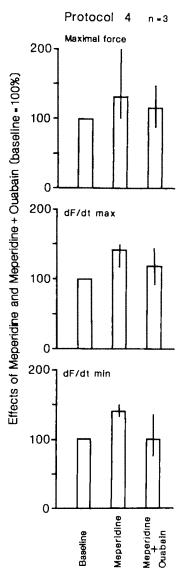


Figure 7. Protocol 3. In three of the experiments from protocol 3 (Figure 6) isoproterenol 5×10^{-8} M was subsequently added. This figure shows that the effects of isoproterenol on maximal force, dF/dt max, and dF/dt min were not attenuated by ouabain and meperidine pretreatment.



<u>Figure 8</u>. Protocol 4. In three experiments, meperidine was added before ouabain. Effects of meperidine and of additional ouabain administration on maximal force, dF/dt max, and dF/dt min are demonstrated.

we observed the development of contracture of the atria.

Discussion

In a previous study (9) we demonstrated that meperidine has a positive inotropic effect on isolated rat atrial muscle at concentrations of 10^{-6} , 5×10^{-6} , 10^{-5} , 5×10^{-5} , and 10^{-4} M and a close to maximal positive inotropic effect was obtained at 10^{-4} M.

In the present study, the positive inotropic effect of 5×10^{-5} M meperidine remained unchanged after blockade of opiate, adrenergic, and histamine receptors, as well as after blockade of slow inward calcium channels. However, the positive inotropic effect was

potentiated after partial blockade of the fast sodium channel by lidocaine, and it disappeared in the presence of ouabain. These observations suggest that the positive inotropic effect of meperidine is related to an increase in intracellular sodium activity rather than to enhanced opening of the slow inward calcium channel.

The positive inotropic effect of meperidine does not appear to be mediated by opiate receptors. The response remained unaltered after blockade with 10⁻⁴ M naloxone. Because the naloxone dose used also blocks α -adrenoceptors (13,14), this finding also precludes α-adrenoceptor stimulation as an important mediating mechanism. Consistent with this is the fact that specific α -adrenoceptor blockade by 10^{-5} M phentolamine did not alter the positive inotropic effect of meperidine. Otherwise, α -adrenergic stimulation would have made a particularly attractive mediating mechanism. Several investigators have demonstrated a moderate increase in contractility during α -adrenergic stimulation (15–17), which also features a small transient decline in contractility before the predominant rise (17,18), as observed with meperidine in the present study.

It is not likely that the positive inotropic effect of meperidine is mediated by enhanced opening of the slow inward calcium channel, because the effect remained unchanged by verapamil. Enhanced opening of the slow inward calcium channel and other changes in intracellular calcium metabolism mediated by β -adrenoceptor-induced stimulation of adenyl cyclase were excluded by β -adrenergic receptor blockade by 5×10^{-6} M propranolol. This finding is also consistent with the effects of H₁ and H₂ blockers. As expected, polaramine enhanced contractility by blocking the inhibitory effect of H₁ stimulation on adenyl cyclase and the cyclic adenosine monophosphate-related actions. Conversely, ranitidine reduced contractility by blocking the H₂-mediated stimulatory effect on adenyl cyclase. These observations indicate some basic level of histamine present during the performance of the present experiments. However, the lack of change in inotropic effect after H₁ and H₂ blockade excludes further release of histamine in the preparation after meperidine as a likely mechanism of enhanced inotropy.

Only the drugs known to alter contractility by changing intracellular sodium activity interfered significantly with the positive inotropic effect of meperidine. After partial blockade of the fast inward sodium channel with lidocaine, the increase in contractility caused by meperidine was significantly higher. This was not because of a lower reference value due to the negative inotropic effect of lidocaine,

as change in contractility was always calculated as a percent of the baseline value before blockers were administered. The greater inotropic effect of meperidine after lidocaine supports the hypothesis of increased inotropy by an increase in intracellular sodium activity. Because lidocaine reduces intracellular sodium activity, there is a greater potential for sodium to increase and to induce an increase in intracellular calcium and, subsequently, in myocardial contractility. Conversely, a high intracellular sodium level caused by a substantial inhibition of the Na,Kpump by subtoxic doses of ouabain seems to leave little room for further increase in contractility by meperidine. However, the observation of no further inotropic effect of meperidine after ouabain does not imply that the ceiling of contractility increase by other mechanisms has been reached. This was confirmed by the further increase in contractility by isoproterenol.

In conclusion, the positive inotropic effect of meperidine appears to be mediated by mechanisms causing an increase in intracellular sodium activity rather than by enhanced opening of the slow inward calcium channel resulting from stimulation of adrenergic or histamine receptors.

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Cooling Potentiates Lidocaine Inhibition of Median Nerve Sensory Fibers

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BUTTERWORTH JF IV, WALKER FO, NEAL JM. Cooling potentiates lidocaine inhibition of median nerve sensory fibers. Anesth Analg 1990;70:507–11.

To determine the effect of cooling on lidocaine potency, nine consenting volunteers underwent bilateral median nerce blocks using 1% lidocaine HCl solution. Room-temperature and ice-cold lidocaine were injected into either dominant or nondominant wrists. Subjects were blinded to the temperature of the anesthetic. Inhibition of $A\alpha$ sensory and motor fibers was assessed as the decline in sensory nerve action potentials and compound motor action potentials, respectively. Inhibition of C fibers was measured as an increase in skin temperature and a decline in galvanic skin potentials. All indices of nerve function demonstrated profound (P < 0.001) time-related changes after injection of local

anesthetic. When ice-cold lidocaine was injected, inhibition of sensory nerve action potentials was significantly greater at all time points (P=0.001) than when room-temperature lidocaine was injected. Inhibition of C fibers as assessed by galvanic skin potentials was marginally faster (P=0.07) when ice-cold lidocaine was used compared with room-temperature lidocaine. No differences between room-temperature and ice-cold lidocaine were observed in inhibition of compound motor action potentials, or in the increase in skin temperature. We conclude that inhibition of median sensory fibers may be increased by cooling 1% lidocaine HCl in an ice bath before injection.

Key Words: ANESTHETICS, LOCAL—lidocaine. TEMPERATURE—local anesthetic action.

Two drawbacks to the use of regional anesthesia are the time required for blocks to become effective after injection of the local anesthetic and the inadequate sensory anesthesia that may sometimes result. Based on studies suggesting that local anesthetic potency is increased at low temperatures (1,2), we anticipated that by cooling a local anesthetic we might increase both the rate of onset and the degree of conduction block. Our data suggest that increased inhibition of sensory nerve fibers results when the 1% lidocaine to be injected is cooled in an ice-water bath before median nerve block at the wrist.

Methods

After review and approval of our study protocol by our Clinical Research Practices Committee, nine consenting (nonpregnant) female volunteers without clinical or electrophysiologic evidence of median nerve dysfunction were prepared for recording of sensory nerve action potentials (SNAPs), compound evoked motor action potentials (CMAPs), galvanic skin potentials (GSPs), and skin temperature (ST). Orthodromic CMAPs and antidromic SNAPs, which reflect function of $A\alpha$ motor and sensory fibers, were elicited simultaneously with supramaximal electrical stimulation of the median nerve 2 cm proximal to the site of anesthetic injection. Compound evoked motor action potentials were recorded with standard abductor pollicis brevis belly tendon surface recordings. Sensory nerve action potentials were recorded with ring electrodes at the base and distal end of the middle finger. Latencies of response were also recorded as the delay between stimuli and the upstroke of CMAP or SNAP.

The GSP was recorded in a median distribution with the active electrode over the distal fingerpad of the middle finger and the reference electrode over the volar aspect of the distal interphalangeal joint, and simultaneously in an ulnar distribution, with electrodes affixed to homologous sites on the little finger. Galvanic skin potential responses were elicited by deep breath, cough, or electrical stimulation. Because

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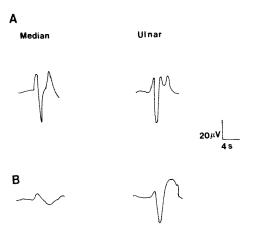
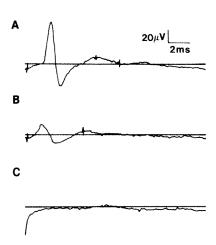


Figure 1. A, Baseline GSPs in both ulnar and median nerve distributions elicited by a deep cough. B, Habituation produces a modest decline in amplitude of ulnar GSPs at the same time that lidocaine inhibits median nerve GSPs. Galvanic skin potential is again elicited by a deep cough. Note the change in ratio between median and ulnar amplitudes in these tracings relative to baseline tracings in 1A. The percent change in this ratio was recorded as the degree of inhibition of the median nerve GSPs due to lidocaine.

GSP is reflexly elicited and habituates with time, a comparative method was devised to evaluate its degree of inhibition by local anesthetic. The ratio of median to ulnar GSP amplitude was calculated at baseline, and the percent change in this ratio was measured at regular intervals after anesthetic injection (Figure 1). Recordings of GSP were made on a Grass (Quincy, Mass.) polygraph with the low-frequency filter cutoff set for 1.6 Hz following the techniques described by Low (3). Skin temperature was measured at baseline and at frequent intervals during the study over the middle fingerpad of the third (median) and little (ulnar) fingers, using a thermistor accurate to 0.1°C.

Clinical observations and ST recordings were all marked on the polygraph (GSP) recording to provide a continuous, concurrent record. Compound evoked motor action potentials, SNAPs, and ST were all elicited and recorded on a single electrodiagnostic instrument (Nicolet Viking, Madison, Wis.). Next, 5 mL of either room temperature (RT) or ice-cold (IC) 1% lidocaine HCl (Astra Pharmaceuticals, Westboro, Mass.) was injected over no less than 45 s through a 22-gauge needle inserted just lateral to the tendon of palmaris longus with its tip beneath the flexor retinaculum. (The RT lidocaine was stored in a pharmacy, the temperature of which varied between 20° and 23.5°C.) Paresthesias were not sought. When paresthesias were elicited, the needle tip was repositioned. When paresthesias were elicited during injection (n = 1), intraneural injection was assumed and the study was discontinued. Recordings (as outlined



<u>Figure 2</u>. Inhibition of the median SNAP by 1% lidocaine at baseline (**A**); 8 min after lidocaine injection—SNAPs have declined by 70% (**B**); and 15.5 min after lidocaine injection—SNAPs have declined by 84% (**C**).

above) were then performed until steady-state values were achieved.

Next, the opposite hand and wrist were prepared as described for injection of either RT or IC lidocaine, whichever was not administered initially. Room temperature and IC lidocaine were injected in either order into either the left or right wrist. Subjects, but not investigators, were blinded to the temperature of the anesthetic solution. However, most subjects could differentiate between RT and IC lidocaine.

Data are presented as mean \pm standard error of the mean (SEM) of the pooled data. Repeated measures analysis of variance was used to assess the effects of (anesthetic) temperature, time (from injection of anesthetic), and any possible interaction between the two factors. The sign test was used to determine the estimated mean time (in minutes) to a 50% reduction in amplitude of GSP.

Results

Data could be recorded from both median nerves in only seven of the nine volunteers; data from two subjects were discarded because of suspected intraneural injection in one case and subject unwillingness to continue with the protocol in the other.

There were significant changes (P < 0.001) across time for all variables (i.e., all declined as the anesthetic took effect). Lidocaine inhibition of GSPs, SNAPs, and CMAPs in a representative subject is illustrated in Figures 1–3. The time-course of mean changes at 5-min intervals in SNAPs, CMAPs, and STs is illustrated in Figures 4–6. No difference could be determined between RT and IC lidocaine in the inhibition of CMAPs or in the local anesthesia-

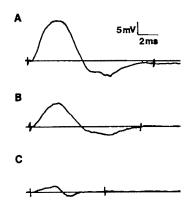
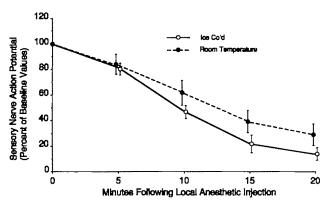


Figure 3. Inhibition of the median nerve CMAP by 1% lidocaine at baseline (A); 8 min after lidocaine injection—the CMAP has declined by 40% (B); and 15.5 min after lidocaine injection—the CMAP has declined by 80% (C).



<u>Figure 4</u>. Time-course of decline of SNAPs after lidocaine injection. All data are expressed as mean \pm sem.

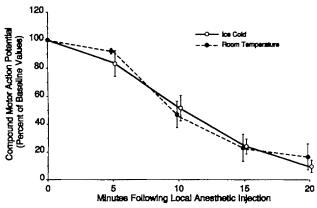


Figure 5. Time-course of decline of CMAPs after lidocaine injection. All data are expressed as mean \pm sem.

induced increase in ST. On the other hand, inhibition of SNAPs was significantly greater (P = 0.001) at all time points (after local anesthetic injection) when IC lidocaine was used rather than RT lidocaine. No interaction between group (IC or RT) and time was detected for any variable.

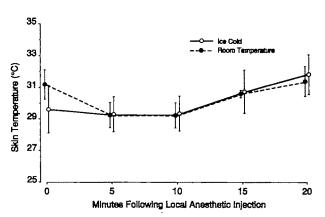


Figure 6. Time-course of ST changes after lidocaine injection. All data are expressed as mean \pm sem.

Because of differences among patients in the timing of data points, GSP could not be plotted in the same manner as the other variables. Using the sign test (pairing the responses of a subject to IC and RT lidocaine) to estimate the median time to a 50% reduction of GSP amplitude, a marginally significant difference (P = 0.07) between groups was identified.

Discussion

Our data demonstrate that onset and degree of block of sensory fibers in the median nerve may be significantly increased by cooling 1% lidocaine in an icewater bath. These results, consistent with animal data and with the known physicochemical characteristics of local anesthetics, suggest that cooling local anesthetics might be a means for hastening the onset of some forms of regional anesthesia.

We assessed the degree of lidocaine inhibition of our subjects' median nerve fiber with electrodiagnostic methods. These represent standard means for assessing nerve conduction failure and are used daily in our laboratory to define peripheral nerve damage. Subjects have difficulty assessing the onset of nerve block. We believe that objective testing is more likely to yield robust numerical data than clinical somesthetic testing.

Our findings contrast with those of Paul et al. (4) and Heavner et al. (5), who found that decreasing anesthetic temperature did not increase the speed of onset or increase the effectiveness of intravenous regional anesthesia (IVRA). However, two important differences between peripheral nerve blocks and IVRA may underlie this apparent conflict. First, local anesthetic solutions are delivered to nerve fibers by the vasculature during IVRA, which is not the case for other regional blocks. Cooling-induced alterations in the vascular distribution of local anesthetic might

delay or prevent the arrival of the anesthetic at its site of action (6). On the other hand, cooling might intensify nerve inhibition during peripheral nerve blocks (in contrast to IVRA) by delaying uptake of local anesthetic from nerve membrane by the peripheral circulation. A second difference between IVRA and other extremity block procedures is the site of local anesthetic action. During peripheral nerve blocks, local anesthetics must penetrate the connective tissue surrounding the nerve trunk and pass superficially located nerve bundles to inhibit axons located throughout the nerve trunk (7). In IVRA, the anesthetic is thought to affect free endings of nerve (8). These differences make it unlikely that any effects of cooling upon membrane permeation, partition coefficients, binding affinities, nerve conduction velocities, pKa, or vascular resistance will alter IVRA and peripheral nerve blocks in an identical manner.

It would seem reasonable that cooling should alter the potency and efficacy with which local anesthetics inhibit impulse conduction. First, cooling produces local anesthesia in and of itself (9,10). Moreover, Goto and Itano have demonstrated that the apparent pKa for lidocaine (at 10^{-3} M) increases from 7.7 at 37°C to 8.4 at 14°C (11). Similar values were obtained by Sanchez et al. (12) and Kamaya et al. (13). Thus, when 1% lidocaine is injected at low temperature, a higher percentage of the local anesthetic will be present in the ionized (protonated) form. Although neutral (free-base) anesthetics permeate membranes more readily than protonated anesthetics and should reach the local anesthetic binding site more rapidly, protonated anesthetics are more potent inhibitors of the Na⁺ channel (for review, see Reference 14). Sanchez et al. (12), using octanol/water partition coefficients to model local anesthetic behavior at the membrane/extracellular fluid interface, have measured decreased partitioning of both the protonated and neutral species into octanol as temperature decreases from 36°C to 26°C. At lower temperatures, due to effects on both ionization and partitioning, concentrations of neutral lidocaine in the membrane phase decline much more than concentrations of protonated lidocaine. Less competition between the less potent neutral form and the more potent (and more prevalent during hypothermia) protonated form may lead to an apparent increase in lidocaine potency, despite an overall decline in total local anesthetic uptake by nerve membranes under hypothermic conditions.

Supporting these physicochemical studies, cooling has been shown to potentiate anesthesia, general and regional, in vitro. Cherkin and Catchpool (15) demonstrated that higher concentrations of diethyl ether,

chloroform, halothane, and methoxyflurane were required to anesthetize goldfish as temperatures increased from 5° to 30°C. More pertinently, Rosenberg and Heavner (1) demonstrated that the nerveblocking concentration of lidocaine increased fourfold as the temperature of rat sciatic nerves in vitro was raised from 17° to 24°C. Finally, Bradley and Richards measured a 50% increase in benzocaine (a permanently neutral local anesthetic; i.e., unlike other clinically useful local anesthetics, benzocaine has no tertiary amine nitrogen to which protons may bind) potency when frog sciatic nerves were cooled from 18° to 2°C (2). On the other hand, cooling anesthetic solutions appears to reduce the extent of neural blockade during spinal anesthesia with 0.5% bupivacaine (16,17). Here, solution temperature modulates the density of the local anesthetic. At body temperature 37°C, 0.5% bupivacaine is hypobaric, whereas at 9°C, bupivacaine is hyperbaric. Thus, when the anesthetic is injected with the patient seated, the warm hypobaric solution produced greater dermatomal spread of the anesthetic. In this circumstance, any greater inhibition of nerve conduction at lower temperature is apparently more than counterbalanced by temperature effects on baricity.

It is difficult to explain why sensory fibers appear more susceptible to the effects of cooling lidocaine than motor fibers. If sensory nerve fibers were located more superficially than motor fibers within the median nerve, sensory fibers might be more susceptible to cooling than motor fibers. The longer delay between anesthetic injection and its arrival at the motor nerve membrane would give a greater opportunity for the anesthetic to be warmed by surrounding tissue and circulating blood. However, topographic studies do not indicate that sensory nerve fibers are consistently located in more superficial locations than motor fibers (18).

Alternatively, fibers with different functions may respond differently to local anesthetics with or without cooling. Differential block, a controversial, poorly defined phenomenon even under the most rigorously controlled experimental conditions, presumably results from differences among nerve fiber types in their susceptibility to local anesthetics (7). Such differences might result from absolute differences in local anesthetic binding affinities, differences in local anesthetic access to binding sites, or differences in conduction safety and mechanisms of impulse blockade. Strichartz and Zimmerman (19) have demonstrated differences in block among different nerve fiber classes with constant anesthetic concentrations but at varying temperatures. Thus, different fiber types may be more susceptible to the combined

effects of lidocaine and hypothermia. Such differences might underlie the differences among fiber types we observed between motor and sensory fibers.

Our conclusion is that a statistically significant increase in the degree of inhibition of median sensory nerve block may be obtained by cooling lidocaine. The differences we measured between IC and RT lidocaine, although small, are similar to those for onset of etidocaine (the local anesthetic of fastest onset) and of bupivacaine (a local anesthetic with very slow onset) ulnar nerve blocks (20). Whether cooling may be safely exploited to expedite other forms of regional anesthesia remains to be shown.

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Postoperative Sore Throat: Effect of Oropharyngeal Airway in Orotracheally Intubated Patients

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MONROE MC, GRAVENSTEIN N, SAGA-RUMLEY S. Postoperative sore throat: effect of oropharyngeal airway in orotracheally intubated patients. Anesth Analg 1990;70:512–6.

The incidence of postoperative sore throat was evaluated prospectively in 203 orotracheally intubated patients undergoing general anesthesia for surgical procedures. Patients were randomly assigned to have either a plastic oropharyngeal airway or a gauze bite-block in place during the operation and were evaluated for the occurrence of postoperative sore throat by questionnaire the day after surgery. The incidence of postoperative sore throat was 35.2% in the oropharyngeal airway group and 42.5% in the gauze bite-block group, not a statistically significant difference (P > 0.05). The incidence of postoperative sore throat was significantly higher when blood was noted on the airway

instruments (64.5%) than when it was not (30.9%) (P < 0.01). There was an association, although not statistically significant, between the incidence of postoperative sore throat and intubation by an anesthesia resident with <1 yr experience (P = 0.064). The data from this study indicate that the intraoperative use of hard plastic oropharyngeal airways, compared with the use of soft gauze bite-blocks, does not increase the incidence of postoperative sore throat. These data also suggest that pharyngeal trauma may contribute significantly to the development of postoperative sore throat. We suggest that aggressive oropharyngeal suctioning may contribute to this pharyngeal trauma.

Key Words: COMPLICATIONS, sore THROAT—pharyngitis, pharyngeal trauma. INTUBATION, TRACHEAL—complications.

Sore throat is a common complaint after general anesthesia. The reported incidence varies widely: 0%–22% in nonintubated patients (1–5) and 6%–100% in intubated patients (1,3,6–14). Although a minor complication, sore throat is a source of considerable discomfort and inconvenience to patients. Numerous studies have shown that the etiology of postoperative sore throat includes size and design of endotracheal tube and cuff, cuff lubricants, cuff pressures, and other factors (3,5,8–16).

The use of the Guedel rubber oropharyngeal airway in nonintubated patients has no effect on the incidence of postoperative sore throat (17). The effect of the use of a hard, plastic, oropharyngeal airway has not been evaluated. We hypothesized that the intraoperative use of a plastic oropharyngeal airway would irritate the posterior pharynx during placement or maintenance and thus cause a greater inci-

dence of postoperative sore throat than would the use of a soft, interdental, gauze bite-block.

Methods

Postoperative sore throat was evaluated prospectively in 203 patients (≥18 yr of age) requiring general endotracheal anesthesia for operative procedures estimated to last 1–3 h. The investigation was approved by the institutional review board and human experimentation committee, and informed consent was waived. Patients who needed a nasogastric tube; who underwent abdominal surgery, except for minilaparotomies and laparoscopies, or head and neck surgery, except for eye surgery; or who required nasotracheal intubation or postoperative intensive care were excluded from the study.

Patients were assigned to have either a hard plastic oropharyngeal airway or an interdental, gauze, roll bite-block inserted during anesthesia according to the last digit of their medical record number: the airway was assigned to patients with odd numbers, and the bite-block to patients with even numbers. The bite-block was made by folding two 10 × 10-cm gauze

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pads in half, rolling them up, and securing them with umbilical tape. All patients underwent orotracheal intubation with cuffed endotracheal tubes with high-volume, low-pressure cuffs (Mallinckrodt). Cuff volumes and pressures were not standardized and no lubricants or local anesthetic ointments were applied to the endotracheal tubes or cuffs.

Patients were anesthetized by anesthesiology residents (supervised by faculty). No attempt was made to standardize the anesthetic technique, except that men were intubated with 8.0-mm endotracheal tubes and women with 7.0-mm endotracheal tubes, and hard, plastic suction devices were not used to suction the airway. If suctioning of the airway or stomach was deemed necessary, flexible suction catheters (Argyle) were used. All patients were supine during the operative procedure.

For each patient, the anesthesiologist recorded patient's age, sex, and smoking history; months of experience of the resident administering anesthesia; difficulty, if any, during intubation; number of laryngoscopy attempts; use of muscle relaxants for intubation; duration of operation; whether coughing or bucking occurred during intubation; and whether there was blood on the laryngoscope blade, oropharyngeal airway, suction catheter, or bite-block. The day after surgery, each patient was given a questionnaire with the following five yes-or-no questions:

Do you have a backache now that you did not have before your operation?

Have you had nausea or vomiting at any time since your operation?

Is your voice hoarse or scratchy? Do you have a sore throat?

Do you have a headache?

Patients were not assisted in filling out the questionnaire or in interpreting the questions; questionnaires for outpatients were completed by telephone interview. The telephone interviewers were specifically instructed not to interpret the questions or to provide guidance in the answers.

The two groups were compared statistically by χ^2 test with Yates' correction; P < 0.05 was considered statistically significant. The data were also analyzed by discriminant analysis to determine whether post-operative sore throat correlated significantly with gender, blood on airway instruments, use of anticholinergic agents, level of resident experience, number of laryngoscopies, or occurrence of bucking during endotracheal intubation.

Results

In the 203 patients studied, a plastic oropharyngeal airway was placed in 102 and a gauze bite-block in 101. The groups were comparable in age, gender, race, smoking history, duration of operation, number of laryngoscopies, frequency of bucking or coughing during tracheal intubation, average months of experience of the anesthesiology resident, use of anticholinergics, and incidence of blood on the airway instrument (P > 0.10); groups were not comparable in the use of succinylcholine (Table 1). According to the questionnaire answers, the incidence of sore throat did not differ significantly between the groups (P =0.28) (Table 2). When data from only those patients in both groups receiving succinylcholine were analyzed, incidence of postoperative sore throat still did not differ significantly between oral airway (28 of 73, 38%) and bite block (40 of 85, 47%) (P = 0.27). The overall incidence of postoperative sore throat was not significantly related to the number of laryngoscopy attempts, anesthesiology resident experience, bucking or coughing during tracheal intubation, use of anticholinergic agents, or gender of the patient (Table 3).

The incidence of postoperative sore throat was greater in patients when blood had been noted on the airway instrument (64.5%) than when this did not occur (30.9%) (P = 0.00003). Of the 47 times blood was noted on an airway instrument, a laryngoscope was involved three times and an oral airway, a bite-block, or a suction catheter the other times. When patients in whom blood was noted on the airway instrument were excluded, the incidence of postoperative sore throat did not differ between oropharyngeal airway (23 of 79, 29%) and bite-block (25 of 76, 33%) (P > 0.05).

Discussion

Numerous authors have suggested that the oropharyngeal airway may cause sore throat (1,3,5,11–15,18,19), and some excluded the use of oropharyngeal airways in their studies (5,10,15). In a study of the effect of the oropharyngeal airway on the incidence of postoperative sore throat during general anesthesia in unintubated patients (17), the incidence of sore throat did not differ statistically significantly between patients who did or did not have a rubber Guedel airway in place during anesthesia. No previous studies of the effect of an oropharyngeal airway on the incidence of postoperative sore throat in intubated patients have been reported. In our study, we attempted to eliminate or control the factors

<u>Table 1</u>. Demographic Comparison of Orotracheally Intubated Patients Undergoing Gynecologic, General, or Orthopedic Surgical Procedures With Oropharyngeal Airway or Bite-Block in Place

	Oropharyngeal airway	Bite-block	P
engreen, and the second	anway	Dite-block	1
Average age (yr)	40.4 ± 15.07	38.9 ± 14.5	
$(mean \pm sb)$			
Gender			
Women (%)	59.8	51.5	0.23
Men (%)	40.1	48.5	0.23
Race			
White (%)	82	1	0.59
Black (%)	17.6	15.8	0.73
Cigarette smokers (%)	18	25.7	0.48
Duration of operation (h) (mean ± sp)	1.95 ± 0.95	1.89 ± 0.86	
> 2 Laryngoscopy attempts (% of patients)	13.7 (14/102)	11.9 (12/104)	
Bucking or coughing during tracheal intubation ^a (%)	40.4 (8/94)	50 (44/88)	0.19
Resident experience (mo)	13.2 ± 8.3	13.1 ± 8.8	
$(mean \pm sd)$			
Succinylcholine ⁴ (%)	<i>7</i> 5	87.5	0.03
Anticholinergics* (%)	41.6	32.6	0.21
Blood on airway instruments* (%)	32.3	42.5	0.33

^{*}Data not reported in all patients.

<u>Table 2</u>. Incidence and Types of Postoperative Complaints Reported on Questionnaire by Patients 24 h After Endotracheal General Anesthesia With an Airway or Bite-Block in Place*

Postoperative	Responses to questi	onnaire
complaint	Oropharyngeal airway	Bite-block
Backache (%)	8	9.9
Headache (%)	11.8	11.8
Hoarseness (%)	46	49 .5
Nausea, vomiting (%)	32.3	34.6
Sore throat (%)	35.2	42.5

 $^{^{\}circ}P = 0.28$ compared with the same complaint with oropharyngeal airway.

previous investigations indicated were associated with postoperative sore throat (1,3–6,8,11–15,17–25).

The only other report besides ours that has related postoperative sore throat to pharyngeal trauma in orotracheally intubated patients was a study of 100 intubated patients in whom extubation was done under direct vision (20). In that study, the pharynx, epiglottis, and glottis were examined for evidence of trauma; in 47 patients in whom trauma was noted, postoperative sore throats developed in 41 (87%). In patients without evidence of trauma, sore throat developed in only 29 of 53 (54%; P < 0.01 by χ^2 analysis with Yates' correction). Thus the data in that study (20) support our data in this study showing that pharyngeal trauma is a significant factor in postoperative sore throat. In our study, the incidence of blood on the laryngoscope blade was low, which suggests the cause of pharyngeal trauma was not related to the intubation itself. We believe that pha-

<u>Table 3.</u> Incidence of Factors Associated With Postoperative Sore Throat in Patients 24 h After Endotracheal General Anesthesia With an Oropharyngeal Airway or a Bite-Block in Place^a

Factor	Sore throat (%)	P
Resident experience		
<1 yr (n=74)	47.3	0.064
>1 yr (n=129)	34	
Blood on airway instruments		
Yes (n = 48)	64.5	0.00003
No $(n = 155)$	30.9	-
Number of laryngoscopies		
1 (n = 176)	38.8	0.905
$\geq 2 (n = 26)$	40.0	
Bucking during intubation		
Yes (n = 85)	36.4	0.661
No $(n = 83)$	39.7	
Anticholinergics		
Yes (n = 63)	38.1	0.64
No $(n = 123)$	40.6	
Gender		
Women $(n = 114)$	44 .7	0.079
Men $(n = 89)$	32.5	

^{*}Data analyzed by discriminant analysis.

ryngeal trauma and, it is likely, a significant portion of postoperative sore throats are associated with suctioning at the end of the procedure, because the suction catheters we used had a stiff, pointed tip that was not vented and thus allowed a high negative pressure to be exerted on airway mucosa. Also, some patients' airways may be more susceptible to trauma than others, which may lead to the development of postoperative sore throat.

In this study, sore throat and resident experience of <1 yr were associated, although not statistically significantly (P=0.064). These data suggest that with a greater number of cases, this association would become significant. It is possible that less experienced residents cause a greater degree of airway trauma during intubation and/or suctioning, which results in postoperative sore throat more frequently than when more experienced residents perform these procedures.

Depending on the method used to identify postoperative sore throat, its incidence varies greatly (4). We determined incidence based on complaints of postoperative sore throat that were detailed in a questionnaire. This method has been demonstrated to be useful in investigations of the influence of anesthetic technique on postanesthetic morbidity (26). The incidence of postoperative sore throat in our study was very similar to that in other studies using questionnaires, a fact demonstrating a reassuring degree of reproducibility (5,27). The positive responses to distraction questions regarding other complaints (headache, backache) were low, and the incidence of nausea and vomiting was similar to that in other studies (28,29), both of which suggest that the data from the questionnaire were reliable.

Although patients who coughed or bucked during tracheal intubation were not excluded from this study, the incidence of bucking and coughing did not differ significantly between the groups (P > 0.2). Because anesthetic technique was not standardized in our study, succinylcholine was used significantly more often (P = 0.030) in patients with bite-blocks than in patients with oropharyngeal airways. In a study in unintubated patients of the effect that succinylcholine administered as an intravenous bolus has in sore throats occurring 24-30 h after the procedure (15), the incidence of postoperative sore throat was significantly higher in patients who received succinylcholine (68% vs 10%) (P < 0.001). However, the number of patients in each group was small (n =20–22), and the method of questioning patients about postoperative sore throat was not standardized; therefore, these data are not conclusive. To ensure that succinylcholine did not affect the results of our study, we also analyzed our data separately for patients given succinylcholine, and there was, again, no significant effect.

We conclude that the intraoperative use of a hard, plastic oropharyngeal airway compared with a soft gauze bite-block does not increase the incidence of postoperative sore throat. However, pharyngeal trauma is a significant factor in postoperative sore throat and is probably caused by aggressive oropharyngeal suctioning measures. We recommend suc-

tioning maneuvers be done carefully. The use of suction catheters with less risk of trauma might decrease the incidence of postoperative sore throat; this deserves further investigation.

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Hearing Loss After Spinal Anesthesia Is Related to Needle Size

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FOG J, WANG LP, SUNDBERG A, MUCCHIANO C. Hearing loss after spinal anesthesia is related to needle size. Anesth Analg 1990;70:517–22.

Audiograms were performed preoperatively and 2 days postoperatively in 28 patients given spinal anesthesia for transurethral resection of the prostate. In 14 patients 22-gauge and in 14 patients 26-gauge spinal needles were used. Hearing loss of 10 dB or more at any frequency was observed in 13 of 14 patients in the 22-gauge group and in 4 of 14 patients in the 26-gauge group. There was a

statistically significant reduction in hearing level in the low-frequency range in patients in whom the 22-gauge needle was used. Hearing loss was unilateral at five frequencies and bilateral at one frequency.

No cases of postspinal headache occurred. Audiometry may be a more sensitive indication of cerebrospinal fluid leak than postspinal headache.

Key Words: ANESTHETIC TECHNIQUES, SPINAL. EAR, HEARING—spinal anesthesia.

Several reports have recently described hearing loss after spinal anesthesia (1–4), suggesting that minor hearing deficits frequently occur (1,4). This complication is in addition to another complication, postspinal headache. The incidence of postspinal headache is recognized as being directly related to the size of the spinal needle used (5,6). Whether hearing loss is a function of the size of the needle used is unknown.

The aim of the present study was to determine the degree of vestibulocochlear dysfunction in patients having spinal anesthesia for transurethral resection of the prostate (TURP) and to determine if the incidence and degree of vestibulocochlear dysfunction are related to the size of the spinal needles used. We also wished to assess any possible correlation between hearing loss and postspinal headache.

Methods

After Ethics Committee approval, informed consent was obtained from 28 patients scheduled for TURP under spinal anesthesia. Exclusion criteria included systemic disorders (apart from arteriosclerosis), a history of deafness, inspissated cerumen, and inability to cooperate during audiometry.

Received from the Department of Anesthesia, Eksjö-Nässjö Hospital, Eksjö, Sweden. Accepted for publication January 2, 1990. Address correspondence to Dr. Sundberg, Department of Anesthesia, Eksjö-Nässjö Hospital, S-575 28 Eksjö, Sweden. The audiologic evaluation consisted of pure tone audiometry using the ascending technique performed by experienced audiometrists. A Madsen OB 70 or OB 522 audiometer (Madsen Electronics, Herlev, Denmark) was used and the system calibrated according to ISO 389, 1975. Audiometry was performed in double-walled silent chambers.

The patients were randomized to receive spinal anesthesia using either a 22-gauge or a 26-gauge spinal needle. On the morning of operation an audiogram was performed in each patient. Premedication followed with 25 mg of meperidine and 10 mg of the sedative dixyrazine (a phenothiazine derivative) given intramuscularly. After intravenous infusion of at least 500 mL of Ringer's lactate solution, spinal anesthesia was administered in the L3-4 interspace using 3.5 mL of 0.5% bupivacaine in 8% glucose. One dural puncture was allowed in each patient; if an additional dural puncture was necessary the patient was removed from the study. The bevel of the needle was inserted parallel to the longitudinal dural fibers. Systolic arterial blood pressure was measured by sphygmomanometry at 5-min intervals during the operation, and any untoward event was recorded. The level of analgesia was estimated by the pin-prick method after 20 min. All patients remained recumbent for the first 12 postoperative hours. On the second postoperative day a second audiogram was performed in each patient under the same conditions as the preoperative examination. The audiometrist

Table 1. Spinal Anesthesia With 22-Gauge Needle

Patient	Age (yr)	Height (cm)	Weight (kg)	Level of analgesia (thoracic segments)	Postoperative systolic blood pressure (mm Hg)	Maximum decrease in systolic blood pressure (mm Hg)	Postoperative headache
1	64	165	54	6	150	40	
2	74	175	86	7	160	50	
3	64	181	<i>7</i> 2	10	120	20	
4	69	178	85	9	140	40	
5	<i>7</i> 9	168	60	7	1 <i>7</i> 0	90	
6	<i>7</i> 8	168	<i>7</i> 8	6	1 6 0	40	
7	64	172	80	7	130	30	
8	67	165	70	5	120	40	
9	62	172	<i>7</i> 5	11	160	30	
10	64	172	65	4	180	65	
11	80	180	96	6	1 <i>7</i> 0	30	
12	51	1 <i>7</i> 3	71	5	120	20	
13	60	173	76	8	130	45	-
14	67	171	88	7	210	60	
Mean ± seм	67.4 ± 2.2	172.4 ± 1.3	75.4 ± 3.0	7.0 ± 0.5	151 ± 7	43 ± 5	

Table 2. Spinal Anesthesia With 26-Gauge Needle

Patient	Age (yr)	Height (cm)	Weight (kg)	Level of analgesia (thoracic segments)	Postoperative systolic blood pressure (mm Hg)	Maximum decrease in systolic blood pressure (mm Hg)	Postoperative headache
1	59	167	69	5	210	45	
2	<i>7</i> 7	176	70	7	180	20	
3	68	181	<i>7</i> 8	6	160	60	
4	61	163	63	8	130	20	
5	67	183	80	6 .	180	60	
6	59	176	90	10	140	30	
7	7 9	171	<i>7</i> 5	7	130	25	
8	67	183	84	7	180	40	
9	<i>7</i> 9	176	78	8	190	50	
10	7 0	181	7 7	10	180	40	
11	<i>7</i> 9	170	67	5	180	60	
12	80	176	72	4	180	70	
13	66	187	<i>7</i> 5	5	180	30	
14	<i>7</i> 9	178	85	6	130	40	
Mean ± sem	70.7 ± 2.2	176.3 ± 1.8	75.9 ± 2.0	6.7 ± 0.5	168 ± 7	42 ± 4	

and the patient were unaware of the needle size used. On the second postoperative day each patient was also examined by an anesthesiologist to determine the presence or absence of postspinal headache or dysfunction of the third, fourth, sixth, seventh, or eighth cranial nerves.

All results are presented as mean \pm sem. In each pair of audiograms from each patient the change in hearing level was calculated at each frequency. The mean change in hearing level for right and left ears respectively for all patients in each of the two groups was calculated at each frequency. A "worse side" was defined as the side on which hearing loss was greater. The results were analyzed for statistical significance using a t-test. Student's t-test for indepen-

dent samples was used to establish the possible statistical significance of demographic and audiometric differences between the groups. P-values of <0.05 were accepted as indicative of statistical significance.

Results

Age, weight, and height were similar in the two groups, as was analgesic level (T7 \pm 2 segments) (Tables 1 and 2). The mean maximum decrease in systolic arterial blood pressure was statistically significant and equal in both groups. No patient had symptoms or laboratory evidence of the "TURsyndrome" (7). No patient complained of postspinal

Table 3. Change of Hearing Level (dB) With 22-Gauge Spinal Needle (Preoperative Minus Postoperative Values)

				F	requency (Hz	:)	-		
Patient	125	250	500	1000	2000	3000	4000	6000	8000
1 R	-10	-5	0	0	-5	-10	25	-50	-60
L	-5	0	-5	5	-15	-5	0	0	0
2 R	0	-10	-5	0	0	0	5	5	-5
L	0	5	0	5	0	0	5	0	0
3 R	0	5	-5	5	5	0	0	-5	-5
L	-10	-5	-10	-5	5	0	-5	-10	0
4 R	0	5	0	0	0	0	10	0	0
L	-10	-5	0	0	5	0	5	0	0
5 R	-10	−5	10	-10	0	-5	−10	15	0
L	-10	−10	0	0	5	-5	−5	0	5
6 R	− 1 5	−15	-10	5	0	-5	-5	0	−15
L	−5	−5	-5	5	-5	0	-5	-10	−20
7 R	5	-5	0	-5	5	0	0	5	-5
L	5	10	0	-10	0	-5	0	15	5
8 R	-10	-5	5	0	0	5	-5	10	5
L	0	-5	5	0	0	5	5	5	5
9 R	0	0	5	0	0	-5	0	5	0
L	5	5	-10	-5	-5	-5	0	5	10
10 R	0	-5	5	5	0	0	0	0	0
L	-5	0	5	0	0	0	0	5	
11 R	-5	-5	-10	-5	0	0	0	-15	−5
L	-10	-5	0	-5	0	0	-5	5	−15
12 R	0	0	5	-5	5	0	5	10	10
L	-10	-10	-10	0	0	5	0	0	0
13 R	0	0	0	0	0	0	-5	0	5
L	0	5	0	0	-10	15	0	0	-10
14 R	0	0	0	0	5	5	0	-5	-10
L	-5	-5	0	0	0	5	5	-5	-10
Mean ± seм R L	-3.2 ± 1.5 -4.3 ± 1.5	-3.3 ± 1.5 -1.8 ± 1.6	0 ± 1.6 -2.9 ± 1.3		1.1 ± 0.8 -2.9 ± 1.4	-1.8 ± 1.0 0 ± 1.5	-2.1 ± 2.2 0 ± 1.1	-1.8 ± 4.2 0.7 ± 1.7	-6.1 ± 4.5 -2.1 ± 2.3
P value R L	<0.05 <0.05	<0.05 NS	NS 0.05	NS <0.05	NS 0.05	<0.05 NS	NS NS	NS NS	NS NS

Negative values indicate decreased hearing. Mean hearing loss in right and left ears is shown at each frequency. R, right ear; L, left ear, NS, not significant.

headache. Apart from the audiometric changes, no postoperative cranial nerve palsies were detected in either group. One patient in the 26-gauge group complained of nausea on the first postoperative day. This was unrelated to posture and was not accompanied by headache.

Audiometric Results

In the 22-gauge group (Table 3), at 125 Hz a statistically significant bilateral hearing loss was observed. At 250 Hz the hearing loss was statistically significant and unilateral, as was the case at 500, 1000, 2000, and

3000 Hz. At higher frequencies no change in hearing level was observed. A decrease in hearing level of 10 dB or more at any frequency occurred in 13 of 14 patients (93%).

In the 26-gauge group (Table 4), at 125 Hz a statistically significant unilateral hearing loss was observed. At frequencies of 3000 Hz and above unilateral increases of hearing level were observed. A decrease in hearing level of 10 dB or more at any frequency was observed in 4 of 14 patients (29%).

The hearing loss on the "worse side" was significantly greater in the 22-gauge group than in the 26-gauge group at 125, 250, 2000, and 3000 Hz (Fig-

Table 4. Change of Hearing Level (dB) With 26-Gauge Spinal Needle (Preoperative Minus Postoperative Values)

				Frequ	iency (Hz)				
Patient	125	250	500	1000	2000	3000	4000	6000	8000
1 R	0	-5	0	0 -5	0 5	-5 5	-5 -5	0 10	0
L	5	0	0						
2 R L	0 -5	0	-5 0	0 0	0 5	0 0	5 5	5 -5	0
3 R	0	5	0	0	0	5	0	0	10
L	-5	-5	-10	-5	-5	0	5	5	-5
4 R	0	-5	0	0	0	0	0	5	0
L	-5	-10	0	0	10	0	5	0	5
5 R	-5	0	5	0	0	0	5	0	0
L	0	0	0	0	0	0	0	0	0
6 R	0	0	5	0	0	0	0	0	10
L	0	0	0	0	5	5	5	0	0
7 R	0	0	-5	0	0	0	5	0	0
L	-5	-5	-5	0	-5	0	-5	0	0
8 R	0	0	5	10	15	5	5	-10	10
L	0	-5	5	5	0	5	0	15	5
9 R	-5	0	0	0	10	5 5	0 5	10 10	15 10
L	5	5	0	0	0				
10 R	0	5	5	0	0 5	0	0 -5	0	10 10
L	10	5	5						
11 R	-5	0	0 5	0	-5 0	5 0	0 5	0	0 -5
L	0	0		-					5
12 R L	0 -10	-5 -5	0 -5	0 -5	5 0	5 0	5 -5	5 5	-10
			5	0	-5	10	5	5	15
13 R L	0	0 10	0	0	<u></u>	10	5	10	-5
14 R	0	0	0	5	0	0	5	-5	5
L	15	10	0	0	10	10	15	0	0
Mean ± seм									
R	-1.1 ± 0.6	-0.4 ± 0.8	1.1 ± 0.9	1.1 ± 0.8	$1.4~\pm~1.4$	2.1 ± 1.0	2.1 ± 0.9	1.1 ± 1.3	5.7 ± 1.6
L	0.4 ± 1.8	0 ± 1.6	-0.4 ± 1.1	-0.7 ± 0.7	1.8 ± 1.3	2.9 ± 1.0	1.4 ± 1.6	3.6 ± 1.5	0.4 ± 1.5
^p value						-0 A#	-0 O**	NG	-0.0E
R	< 0.05	NS NS	NS NS	NS NS	NS NS	<0.05 <0.05	<0.05 NS	NS <0.05	<0.05 NS
L	NS	NS	IND.	CNI	CNI	~0.03	193	~0.03	INU

Negative values indicate decreased hearing. Mean hearing loss in right and left ears is shown at each frequency. R, right ear; L, left ear; NS, not significant.

ures 1 and 2). Intergroup differences were of no statistical significance at other frequencies.

Discussion

The previously reported incidence of vestibulocochlear dysfunction after spinal anesthesia varies between 0.2% and 8% (4,6), based on the incidence with which patients complained of deafness (i.e., a major hearing deficit). However, minor hearing deficits after spinal anesthesia have been observed on the second postoperative day in 42% of patients who underwent TURP (1).

Hearing deficits after spinal anesthesia are transient, although they may take several months to disappear (1–4,6,8). Major hearing deficits have been reported in association with postspinal headache (2,6,8); minor auditory losses are usually unaccompanied by postspinal headache (1). In this study, the hearing deficits were small and of minor clinical importance.

The etiology of vestibulocochlear disturbances after spinal anesthesia is not clear. It is possible that the decrease in cerebrospinal fluid pressure that follows dural puncture may be transmitted through the cochlear aqueduct to the inner ear, thus resulting in an

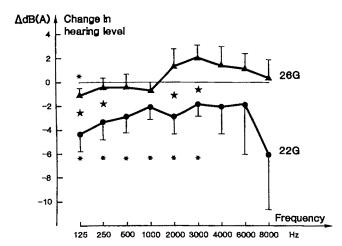


Figure 1. Mean change in hearing level ± sem on "worse side" is shown at each frequency. Negative values indicate decreased hearing. *Statistically significant change in hearing level compared with preoperative values. ★, Statistically significant intergroup difference.

endolymphatic hydrops. The resulting distortion of the membranous labyrinth may be accompanied by displacement of Reissner's membrane into the scala vestibuli (9). It is generally accepted that the endolymphatic hydrops is involved in the pathogenesis of Ménière's disease (9,10). Audiometric studies of patients suffering from Ménière's disease indicate that the early changes in hearing level occur in the low-frequency range (9,11), and that the initial hearing loss may be unilateral (9,11). The unilaterality in itself cannot be explained. The finding of this study that the hearing loss was located in the low-frequency range is in accordance with previous reports (1-4). One patient in the 22-gauge group developed a hearing loss of \geq 25 dB at frequencies of 4 kHz and above. The nature of this major hearing deficit is presumably unrelated to the spinal anesthesia per se. As the tone range of speech is 500-2000 Hz, the patient experienced no difficulties in communicating postoperatively.

In a recent study by Wang et al. (1) the effect of spinal anesthesia and epidural anesthesia on vestibulocochlear function was examined. All patients were scheduled for TURP, and demographic data for the groups were similar to those of this study. The preoperative routines and the audiometric evaluations were identical to those of this study. No statistically significant hearing loss was demonstrated in the epidural group at any frequency. There was no statistically significant difference between the epidural group in that study (1) and the 26-gauge group in this study, i.e., hearing level seems to be unaffected by epidural anesthesia and by spinal anesthesia using a 26-gauge needle.

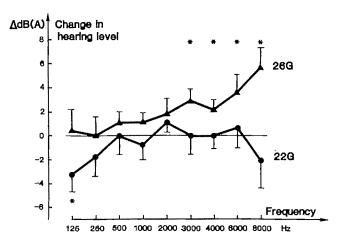


Figure 2. Mean change in hearing level \pm SEM on "better side" is shown at each frequency. Negative values indicate decreased hearing. *Statistically significant change in hearing level compared with preoperative values.

In the two groups of this study, an increase in hearing level was observed in some patients in the high-frequency range. Similar observations were found in both groups in a previous study of epidural and spinal anesthesia (1). The nature of this observation is difficult to explain. Most of the investigated older population had audiometric signs of presbyacusis, i.e., hearing loss in the high-tone range. It is possible that this may predispose the patients to greater fluctuations in hearing level after spinal anesthesia than would occur in younger patients.

Postspinal headache is generally attributed to decreased intracranial pressure caused by leakage of cerebrospinal fluid through the dural puncture (5,6,8,12,13). The incidence of postspinal headache is related to the diameter of the needle used for the dural puncture (5,6,8,12,13). Large populations are required to demonstrate differences in the incidence of postspinal headache, especially in older people (5,8,14). However, in this study differences in hearing ability without concurrent postspinal headaches were demonstrated when needles of different size were used in a relatively small patient population.

The present study was limited to the first 2 days postoperatively because of the early discharge of patients from this hospital. Although the majority of cases of postspinal headache develop within 2 days of spinal anesthesia (2,6,8,14), it is possible that some potential cases of postspinal headache were missed.

Because the two groups were similar in the degree of systolic hypotension, the dose of bupivacaine used, age, weight, height, and level of sensory blockade, the most likely explanation for the observed hearing changes is that differences in needle sizes caused differences in the size of the dural tears allowing cerebrospinal fluid leakage to alter the cerebrospinal fluid pressure. Studies of fresh cadaver dura punctured by different sizes of spinal needles support this explanation (15).

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Blood Gas Analysis of Mixed Venous Blood During Normoxic Acute Isovolemic Hemodilution in Pigs

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TROUWBORST A, TENBRINCK R, VAN WOERKENS ECSM. Blood gas analysis of mixed venous blood during normoxic acute isovolemic hemodilution in pigs. Anesth Analg 1990;70:523–9.

Mixed venous oxygen saturation of hemoglobin (Svo_2) and mixed venous oxygen tension (Pvo_2) may reflect the overall balance between oxygen consumption and delivery. Because of the potential value of monitoring Svo_2 and Pvo_2 as indications of the state of tissue oxygenation, the aim of this study was to determine, during normoxic acute isovolemic hemodilution in pigs, the critical Pvo_2 , critical Svo_2 , and critical oxygen extraction ratio (ER) at which oxygen uptake starts to decline during further induced hemodilution.

During stepwise induced isovolemic hemodilution, a gradual decline in SvO2 and PvO2 was observed in all

animals. The mean \pm SD of the critical PvO_2 of six animals was 32.3 ± 3.1 mm Hg. The mean \pm SD of the critical SvO_2 was $44.2\% \pm 7.9\%$. The ER increased gradually. At an ER of 0.57 ± 0.08 , oxygen uptake started to decline. A significant correlation was found between changes in SvO_2 and changes in ER. These degrees of hemodilution were accompanied by an increase in cardiac index, pulmonary wedge pressure, heart rate, and left ventricular stroke work index. Only a slight decrease in systemic vascular resistance was observed. We conclude that measurements of PvO_2 and SvO_2 can be used as indicators of the critical point of hemodilution and that the SvO_2 during hemodilution reflects the overall balance between oxygen uptake and oxygen delivery, confirmed by the strong correlation found between SvO_2 and oxygen extraction ratio:

Key Words: BLOOD, HEMODILUTION—isovolemic.

The mixed venous oxygen saturation of hemoglobin (Svo₂) and the mixed venous oxygen tension (Pvo₂) reflect, under certain circumstances, the state of tissue oxygenation. Changes in cardiac output (CO), arterial oxygen content, and oxygen uptake (Vo₂) influence these parameters (1). To our knowledge, there are only two reports of Pvo₂ studies during hemodilution. In one, during hypovolemia produced in dogs by removal of blood the critical Pvo₂ at which Vo₂ began to decrease was found to be 29.9 mm Hg (2). In the other study, the critical Pvo₂ in dogs during isovolemic induced anemic hypoxia was 44.8 torr (3). In both studies, the Svo₂ at the point at which Pvo₂ had so decreased that Vo₂ started to decrease during hemodilution is not mentioned. In several

clinical situations hemodilution is beneficial, as it reduces the risks associated with the transfusion of homologous blood (4–7). Because of the possible value of monitoring Svo₂ and Pvo₂ in the evaluation of tissue oxygenation during hemodilution, the aim of this study was to determine, during normoxic acute isovolemic hemodilution in sedated paralyzed pigs, the critical Pvo₂, the critical Svo₂, and the critical oxygen extraction ratio (ER) at which Vo₂ starts to decline with further hemodilution.

Methods

This protocol was approved by the Animal Care and Use Committee of the Erasmus University, Rotterdam, The Netherlands.

Six male Yorkshire pigs (10.2–12.0 kg) were used. After giving 0.3 mg/kg midazolam intramuscularly, a catheter was introduced into one of the ear veins and the trachea was intubated. Throughout the experimental procedure sedation was maintained with a continuous intravenous infusion of 0.2 mg·kg⁻¹·h⁻¹

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midazolam. After intubation of the trachea 0.1 mg/kg pancuronium was given intravenously with an additional continuous intravenous infusion of 0.3 mg·kg⁻¹·h⁻¹. The pigs' lungs were then ventilated with air, using tidal volumes adequate to maintain end-tidal CO₂ between 4.5 and 5.0 kPa (33 and 38 mm Hg). Catheters were placed in the left femoral artery, the right femoral vein, and the right femoral artery (the latter for arterial blood pressure monitoring). Via the left femoral vein a thermodilution catheter (Swan Ganz 93A-095-7F) was introduced into a pulmonary artery. In all animals the injectate port was located in the right atrium as proven on postmortem examination. The urinary bladder was catheterized. Body temperature (blood temperature) was measured with the thermistor electrode of the thermodilution catheter and was kept stable throughout the procedure by means of a heating pad. After all preparations were completed, the sedated paralyzed animals were ventilated until blood gas tensions, pH, and hemodynamic parameters were stabilized (average time 30 min). Pulse rate, arterial blood pressures, pulmonary arterial pressures, and the right atrial pressure were monitored continuously (Horizon 2000, Mennen Medical, Israel). After the stabilization period baseline measurements were made, including heart rate, mean arterial blood pressure, systolic pulmonary arterial pressure, diastolic pulmonary arterial pressure, pulmonary wedge pressure, right atrial pressure, and CO. In addition, arterial and mixed venous blood samples were taken for measurements of Po₂, pH, and Pco₂ (ABL 330, Radiometer, Copenhagen) and for measurement of hemoglobin and oxyhemoglobin content (Spectrophotometer OSM3, Radiometer, Copenhagen). Oxygen flux (O2 flux) was calculated as the product of arterial oxygen content and CO. Oxygen uptake by the tissue (Vo₂) was defined as the product of CO and the arteriovenous oxygen content difference. The ER was calculated as Vo₂ divided by O2 flux.

The first step of isovolemic hemodilution with isooncotic dextran 40, 50 g/L in 0.9% salt solution (Isodex, NPBI, The Netherlands) began after baseline measurements were completed. The dextran solution (warmed to 38°C) was instilled slowly into the right femoral vein at the same time and at the same rate that blood was removed from the left femoral artery. Stepwise isovolemic hemodilution was induced by steps of 10 mL/kg until a total exchange of 40 mL/kg had been reached and afterwards by steps of 5 mL/kg. New sets of data were obtained after each step of isovolemic hemodilution when blood gas tension, pH, and hemodynamic parameters were

stabilized again (average time 5 min). The time between each step of blood exchange was 15 min.

To establish the mean critical $\text{Pvo}_2 \pm \text{sd}$, Vo_2 was plotted against the Pvo_2 in each animal. The critical point of Pvo_2 after which Vo_2 gradually decreased was analytically chosen from the intersection of the two best-fit regression lines, determined by a least sum of squares technique as described by Schumacker et al. (2). The mean \pm sd of the Pvo_2 at this critical point was defined as the critical $\text{Pvo}_2 \pm \text{sd}$. The critical Svo_2 and critical ER were also determined by the same least sum of squares technique.

All values are expressed as mean \pm sp. In each figure the same animals are presented in the same order. The accepted probability for a statistical significance between means was P < 0.05. The statistical significance of differences was tested by the Wilcoxon signed-rank test. Regression lines were estimated by methods of least squares. For regression analysis, the Spearman rank correlation coefficient was used.

Results

Hemodynamic Responses

During hemodilution there was a significant increase in cardiac index (CI) of up to >40% (Table 1). The CI did not return to baseline values. Even at a blood exchange of 100 mL/kg the CI increased 30% above baseline values; at the same time total peripheral vascular resistance (SVR) decreased only slightly (by 10%–15%). Left ventricular stroke work index increased 45%, accompanied by an increase of 30% in heart rate. A gradual increase in pulmonary wedge pressure up to 40% above baseline values was observed, presumably due to an increase in venous return to the heart.

In each animal, there was a gradual decline in Pvo₂ during stepwise induced hemodilution. When Vo₂ was plotted against Pvo₂ in each animal, the critical Pvo₂ at which Vo₂ starts to decline could be established from the intersection of the two best-fit regression lines (Figure 1). The mean of the critical Pvo₂ of the six animals was 32.3 ± 3.1 mm Hg. The mean critical Svo_2 was 44.2 ± 7.9 (Figure 2). Plotting the Vo₂ against the ER in each animal gives a critical ER value of 0.57 ± 0.08 (Figure 3). During hemodilution a direct correlation was found between the Svo₂ and the critical ER value (Figure 4). Hemodilution up to a 100-mL/kg exchange of blood volume did not significantly alter the arterial pH, Po2, or Pco2. The baseline pH in the mixed venous blood was 7.41 ± 0.02 ; with 100-mL/kg blood exchange it was 7.35 ± 0.05 . Levels of mixed venous pH, Pvo₂, Svo₂, O₂ flux, Vo₂,

Table 1. Hemodynamic Responses After Each Step of Blood Exchange

T	1		ا ر						
Blood exchange	MAP	MPAP	PWP	HR	ם	LVSWI	SVR	PVR	
(mL/kg body wt)	(mm Hg)	(mm Hg)	(mm Hg)	(beats/min)	$(L \cdot min^{-1} \cdot m^{-2})$	$(g \cdot cm^{-1} \cdot m^{-2})$	$(dyne \cdot s^{-1} \cdot cm^{-5})$	$(dyne \cdot s^{-1} \cdot cm^{-5})$	Hct
0 (baseline)	96 ± 13	17.7 ± 4.5	7.8 ± 6.6	167 ± 20	5.1 ± 1.0	34.0 ± 8.9	3538 ± 1101	482 ± 163	30.0 ± 3.6
10	98 ± 10	18.5 ± 2.6	8.8 ± 7.0	185 ± 33	5.7 ± 0.7	35.1 ± 8.4	3196 ± 987	429 ± 63	23.7 ± 2.2
82	109 ± 14	22.0 ± 5.2	10.3 ± 8.8	196 ± 27	6.8 ± 1.1^{4}	44.9 ± 12.2	2945 ± 722	424 ± 105	$20.1 \pm 1.8^{\circ}$
30	114 ± 9	23.3 ± 5.1	9.0 ± 9.5	213 ± 15^{4}	6.8 ± 1.1^{4}	$46.7 \pm 13.3^{\circ}$	3141 ± 1037	410 ± 81	18.3 ± 2.2
40	117 ± 9	23.8 ± 3.6	9.7 ± 8.2^{4}	$216 \pm 15^{\circ}$	$7.2 \pm 0.9^{\circ}$	47.3 ± 14.4^{4}	3037 ± 937	466 ± 223	$15.6 \pm 1.5^{\circ}$
55	117 ± 8	24.2 ± 3.1^{4}	$10.5 \pm 6.9^{\circ}$	$210 \pm 15^{\circ}$	7.3 ± 0.8^{4}	$48.9 \pm 16.6^{\circ}$	3049 ± 994⁴	490 ± 248	$13.2 \pm 0.8^{\circ}$
9	116 ± 13^{4}	$23.5 \pm 3.8^{\circ}$	$10.2 \pm 6.5^{\circ}$	208 ± 18	7.1 ± 0.6^{4}	47.7 ± 14.7	3147 ± 1123	468 ± 211	12.0 ± 1.1^{4}
65	$115 \pm 10^{\circ}$	23.3 ± 3.9	+1	206 ± 19	7.1 ± 0.8	$47.1 \pm 15.3^{\circ}$	3087 ± 964	428 ± 162	10.8 ± 0.8^{4}
70	116 ± 11^{4}	23.3 ± 4.4	11.0 ± 6.6	201 ± 23	7.1 ± 0.9	$49.6 \pm 17.3^{\circ}$	3130 ± 1069	427 ± 191	9.8 ± 0.6^{4}
75	114 ± 11^{4}	23.3 ± 4.6	$11.0 \pm 6.5^{\circ}$	+1	$7.0 \pm 1.0^{\circ}$	46.1 ± 15.1^{4}	3095 ± 963	429 ± 141	$9.7 \pm 0.8^{\circ}$
80	111 ± 12	22.2 ± 4.2	9.8 ± 6.6°	202 ± 17	6.8 ± 0.8	$47.3 \pm 14.2^{\circ}$	3132 ± 1079	445 ± 205	9.0 ± 1.2^{e}
85	108 ± 12	22.5 ± 3.9	$10.5 \pm 6.9^{\circ}$	201 ± 19	$6.8 \pm 0.8^{\circ}$	44.4 ± 17.1	3008 ± 1024	435 ± 175	8.4 ± 0.8^{4}
06	104 ± 9	21.5 ± 3.8	$9.8 \pm 5.4^{\circ}$	205 ± 20	6.7 ± 0.7	40.7 ± 15.1	2960 ± 1130^{4}	416 ± 191	7.8 ± 0.9^{4}
95	8 + 86	21.0 ± 2.9	$10.5 \pm 5.9^{\circ}$	197 ± 20	6.6 ± 0.7	38.2 ± 10.2	$2724 \pm 857^{\circ}$	389 ± 111	6.9 ± 0.7
100	91 ± 10	20.7 ± 3.9	11.0 ± 5.2	200 ± 18	6.6 ± 0.9^{4}	34.4 ± 13.1	2580 ± 807	$364 \pm 105^{\circ}$	6.6 ± 0.8
CI, cardiac index;	Hct, hematocrit	HR, heart rate; LV5	WI, left ventricular	stroke work index	, MAP, mean arterial	blood pressure; MP/	AP, mean pulmonary ar	Cl. cardiac index; Hct, hematocrit, HR, heart rate; LVSWI, left ventricular stroke work index; MAP, mean arterial blood pressure; MPAP, mean pulmonary artery pressure; PVR, pulmonary vascular	monary vascular

CJ, Cardiac nices, 12tc, irenances, 12tc, 15tenances, 17WP, pulmonary wedge pressure; 5VR, systemic vascular resistance. Yalues are mean ± 3D (n = 6).

P < 0.05 in comparison to baseline.

and the ER after each step of induced hemodilution are summarized in Table 2.

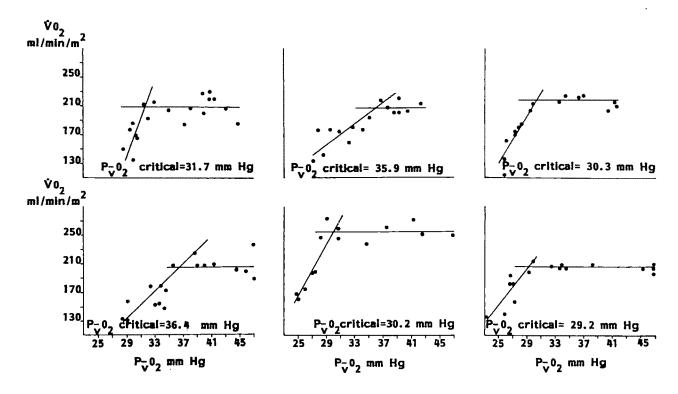
Discussion

Yorkshire pigs were chosen for this study because the pig is so closely related to the human, anatomically and physiologically. The cardiovascular system and metabolism of pigs and humans show similarities with respect to the size and distribution of coronary vessels, blood pressure, heart rate, CI, regional distribution of CO, and maximum oxygen consumption (8–10).

Continuous monitoring of Svo₂ has been used as an indicator of the effects of various therapeutic maneuvers in critically ill patients, as a predictor in hemodynamically unstable patients, and for measurement of oxygen transport patterns (11–13). In a prospective study, Svo₂ was found to correlate well with the oxygen utilization coefficient; Svo₂ therefore reflects the overall balance between oxygen consumption and delivery in critically ill surgical patients (14).

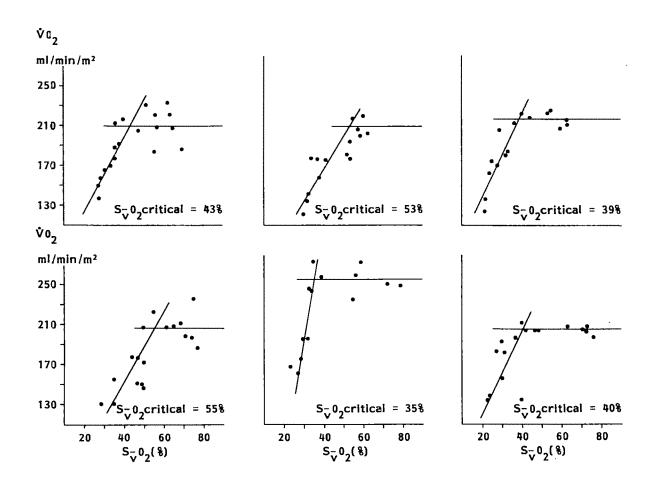
To our knowledge, no reports are available concerning Svo_2 during isovolemic hemodilution, or concerning the critical Svo_2 at which Vo_2 starts to decline during further stepwise induced hemodilution. In this study, the effect of a decrease in oxygen supply on oxygen uptake during normoxic acute isovolemic hemodilution started when Svo_2 was $44.2\% \pm 7.9\%$. As in the prospective study in critically ill patients (14), we found a direct correlation between the Svo_2 and the ER during a stepwise induced hemodilution.

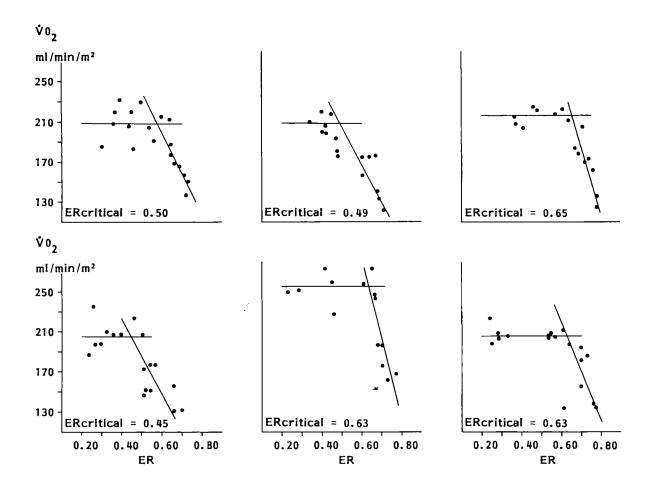
Another parameter studied by us is the critical Pvo₂. In our study, the critical Pvo₂ at which Vo₂ became dependent on oxygen flux was 32.3 ± 3.1 torr. To our knowledge, in only two other studies one during isovolemic hemodilution, the other during hypovolemic hemorrhage—is the critical Pvo₂ reported. During hypovolemic hemorrhage in dogs, a critical Pvo_2 of 29.9 \pm 2.3 was found (2). These data, however, cannot be compared with our data because of the differences in experimental procedure (hypovolemia via removal of blood volume with a fixed arterial oxygen content versus isovolemic hemodilution and consequent decreased arterial oxygen content). In the other study using dogs, Cain reported a critical Pvo₂ of 44.8 torr during isovolemic induced anemic hypoxia, at which point oxygen uptake began to decrease (3). The large difference between the results of Cain's study and ours may be explained in two ways. First, the critical Pvo₂ in Cain's study was



<u>Figure 1</u>. Vo₂ plotted against Pvo₂ in each animal. The mean Pvo₂ critical was 32.88 \pm 3.10 mm Hg.

Figure 2. Vo_2 plotted Svo_2 in each animal. The mean Svo_2 critical is 44.2% \pm 7.9%.





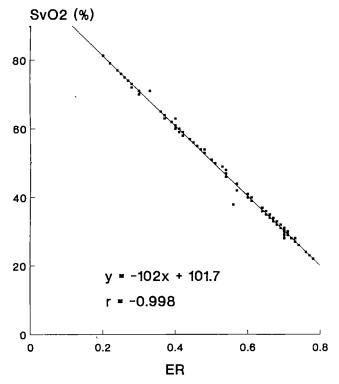


Figure 4. Scatterplot of Svo₂ against the ER.

Figure 3. Vo_2 plotted against ER in each animal. The mean ER critical is 0.57 ± 0.08 .

identified in a different manner. The percentage change in Vo₂ in comparison to the control Vo₂ was plotted against the Pvo₂ to obtain the critical Pvo₂. The single linear regression line obtained in this way was intersected with the point of 100% oxygen uptake, placing more weight on the value of the baseline Vo₂ and less on the observed increase in Vo₂ at the initial stage of hemodilution.

The other reason for the observed differences in critical Pvo₂ during hemodilution may be the differences in cardiovascular and sympathetic responses between dogs and pigs and the differences in the anatomy and distribution of coronary arteries in both animals (8,10). The difference in responses of CI and SVR on hemodilution between Cain's report and our study supports this hypothesis. In our study, a 40% increase in CI was observed. The percentage increase in CO in dogs in comparison to the values obtained before isovolemic anemia was induced was more pronounced in Cain's study (130%). Cain observed a decrease in SVR of 60% at the initial stage of iso-

Table 2. Systemic Oxygenation and Mixed Venous Blood Oxygenation After Each Step of Blood Exchange

Blood exchange		Pvo,				O, Flux	Vo	
(mL/kg body wt)	Hb (g%)	(mm Ĥg)	Svo ₂ (%)	pHa	pHv	$(mL.min^{-1}.m^{-2})$	$(mL.min^{-1}.m^{-2})$	ER
0 (baseline)	10.0 ± 1.2	45.2 ± 4.8	70.3 ± 8.1	7.45 ± 0.03	7.41 ± 0.02	738 ± 202	+	0.30 ± 0.08
10	$7.9 \pm 0.8^{\circ}$	44.4 ± 4.1	68.8 ± 7.4	7.45 ± 0.03	7.41 ± 0.02	649 ± 123	200 ± 11	0.32 ± 0.07
8	6.7 ± 0.7	43.9 ± 3.6	67.5 ± 7.3	7.44 ± 0.02	7.41 ± 0.02	669 ± 157	201 ± 50	0.33 ± 0.07
8	$6.1 \pm 0.8^{\circ}$	40.9 ± 3.5^{4}	+1	7.45 ± 0.02	7.42 ± 0.02	593 ± 101	221 ± 27	0.38 ± 0.07
\$	$5.2 \pm 0.5^{\circ}$	40.5 ± 4.1	$60.1 \pm 6.8^{\circ}$	7.44 ± 0.01	7.41 ± 0.02	539 ± 65	220 ± 21	0.42 ± 0.04
5 <u>c</u>	4.4 ± 0.3^{4}	37.3 ± 2.9	54.9 ± 7.0°	7.45 ± 0.02	7.41 ± 0.02	464 ± 47°	213 ± 19	$0.46 \pm 0.06^{\circ}$
99	4.0 ± 0.4	$34.2 \pm 3.5^{\circ}$	$47.9 \pm 8.4^{\circ}$	7.45 ± 0.03	7.40 ± 0.03	+1	213 ± 27	$0.53 \pm 0.08^{\circ}$
65	$3.6 \pm 0.3^{\circ}$	32.9 ± 2.9^{e}	$43.6 \pm 7.8^{\circ}$	7.44 ± 0.03	7.40 ± 0.03	$375 \pm 45^{\circ}$	213 ± 32	0.56 ± 0.07
70	3.3 ± 0.2^{4}	32.0 ± 2.4	$42.1 \pm 7.8^{\circ}$	7.44 ± 0.02	7.40 ± 0.02	H	H	0.59 ± 0.08^{4}
73	3.3 ± 0.3	$31.1 \pm 2.6^{\circ}$	+1	7.44 ± 0.03	7.40 ± 0.03	+1	192 ± 32	0.59 ± 0.07
88	3.0 ± 0.4	H	37.4 ± 6.8	7.44 ± 0.02	7.40 ± 0.02	+1	H	0.63 ± 0.06 °
85	$2.8 \pm 0.3^{\circ}$	29.6 ± 2.6	$35.8 \pm 8.4^{\circ}$	7.43 ± 0.03	7.39 ± 0.03	$280 \pm 25^{\circ}$	$180 \pm 19^{\circ}$	$0.65 \pm 0.08^{\circ}$
8	$2.6 \pm 0.3^{\circ}$	H	33.4 ± 8.1 *	7.44 ± 0.01	H	260 ± 25"	H	0.67 ± 0.07
8	2.3 ± 0.3^{4}	28.3 ± 2.9	32.6 ± 4.0°	7.42 ± 0.03	7.36 ± 0.04	234 ± 41°	156 ± 18	$0.68 \pm 0.08^{\circ}$
100	2.2 ± 0.3^{4}	27.4 ± 2.1^4	28.3 ± 5.2	7.41 ± 0.04	$7.35 \pm 0.05^{\circ}$	$216 \pm 34^{\circ}$	155 ± 23°	$0.72 \pm 0.05^{\circ}$
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oxygen extraction ratio, Hb, hemoglobin; pHa, arterlal pH; pHv, mixed venous pH; PvO2, mixed venous oxygen tension; SvO2, mixed venous oxygen saturation of hemoglobin; VO2, oxygen uptake lues are mean \pm sD (n = 6). < 0.05 in comparison to baseline volemic induced anemic hypoxia and of 74% at the final stage, whereas in our study in pigs the decrease in SVR was not more than 10%–15% of the baseline value. Only in the final stage of anemic hypoxia during isovolemic hemodilution was the decrease in SVR enhanced to 25%—probably because at that moment the hypoxic induced vasodilation became more dominant than the reported reflex vasoconstrictor activity during anemia (15).

The differences in cardiovascular and hemodynamic responses between pig and dog may also explain the difference in critical ER in the two species (and in the two studies). In dogs, a critical ER value of 0.79 has been reported (16), whereas in our study of pigs, the ER level was 0.57 when whole body oxygen uptake started to decline.

Because of the strong correlation found between Svo_2 and ER, we suggest that the monitoring of Svo_2 may be important as an indicator of the state of tissue oxygenation during normovolemic hemodilution. In sedated, paralyzed pigs a critical Svo_2 of $44.2\% \pm 7.9\%$ and a critical Pvo_2 of 32.28 ± 3.10 mm Hg was found, at which point oxygen uptake started to decline during further hemodilution.

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Effect of Enflurane on Contractile Reactivity in Isolated Canine Mesenteric Arteries and Veins

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KOBAYASHI Y, YOSHIDA K-I, NOGUCHI M, WAKASUGI Y, ITO H, OKABE E. Effect of enflurane on contractile reactivity in isolated canine mesenteric arteries and veins. Anesth Analg 1990;70:530–6.

The effects of enflurane on responses of isolated canine mesenteric arteries and veins to transmural nerve stimulation and to exogenously administered norepinephrine (a mixed α_1 - and α_2 -adrenoceptor agonist), phenylephrine (a selective α_1 -adrenoceptor agonist), and tyramine were studied. The contractile responses of the arteries and the veins to transmural nerve stimulation and to norepinephrine were attenuated by exposure to enflurane; the responses to phenylephrine were decreased more than those to norepinephrine. When compared with the effect of enflurane on

transmural nerve stimulation-induced responses, exposure to enflurane resulted in slight attenuation of the contractile responses caused by tyramine, suggesting that enflurane may inhibit the responses to tyramine by interfering with an interaction between released norepinephrine and postjunctional α_1 -adrenoceptors rather than with tyramine-induced norepinephrine release. The data are also consistent with the view that enflurane acts on sympathetic nerve endings to inhibit release of norepinephrine associated with electrical stimulation-induced nerve membrane depolarization.

Key Words: ANESTHETICS, volatile—enflurane. MUSCLE, smooth—vascular. ARTERIES, ENFLURANE EFFECTS. VEINS, ENFLURANE EFFECTS.

The ability of the volatile anesthetics halothane and enflurane to depress arterial pressure has been attributed to depressed contractile performance of heart muscle (1), inhibition of norepinephrine release from the adrenal medulla (2), decreased sympathetic vasoconstrictor tone (3), and a direct depressant effect on vascular smooth muscle cells (4). Rorie et al. (5) suggested that halothane decreases the stimulationevoked release of norepinephrine by stimulation of prejunctional inhibitory muscarinic receptors. Although halothane and enflurane are halogenated hydrocarbons that have similar pharmacologic properties, it may not be valid to conclude that enflurane has the same effect on the peripheral nervous pathways as does halothane. As the effect of enflurane on vascular smooth muscle has not, to the best of our knowledge, been reported in the literature, we undertook a study of the effect of enflurane on adrenergic neuroeffector transmission in isolated canine mesenteric arteries and veins. We found that enflurane can inhibit norepinephrine release from sympathetic nerve endings and interfere with postjunctional receptor-mediated contractile responses of the vessels to norepinephrine.

Methods

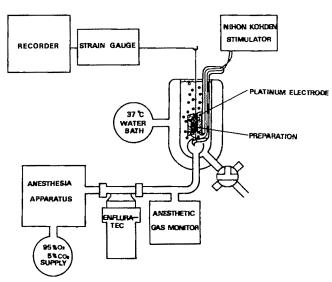
Vessel Collection, Preparation, and Stimulation

Mesenteric arteries and veins were taken from mongrel dogs of either sex (7–15 kg) after exsanguination during anesthesia with sodium pentobarbital (30 mg/kg IV). The blood vessels were cleaned of adherent connective tissue and cut into rings (2–3 mm) without disturbing the intimal layer. The rings were studied in organ chambers gassed with 95% O₂–5% CO₂ (37°C, pH 7.4) containing 20 mL of modified Krebs–Ringer solution of the following composition in millimolars: NaCl, 128.0; KCl, 4.9; MgCl₂, 1.2; CaCl₂, 1.6; NaHCO₃, 14.8; NaH₂PO₄, 1.18; dextrose, 10.0; and calcium disodium ethylenediaminetetraacetic acid, 0.026. Each ring was suspended in the water-jacketed

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<u>Figure 1</u>. Schematic illustration of the experimental setup. For details see text.

organ chamber. One end of the preparation was connected with 4-0 surgical suture (Ethicon, silk) to a force transducer (Nihon Kohden, TB-612-T); changes in isometric force were recorded using an amplifier (Nihon Kohden, AP-601-G) attached to a recorder (Nihon Kohden, PJ-681-G). Resting tensions were adjusted to 1.5 and 2.0 g for the veins and the arteries, respectively. Before the start of the experiment, the preparations were allowed to equilibrate for 120 min in control media, during which time the solutions were replaced every 10 or 15 min.

The tissue preparations were placed between a pair of rectangular platinum electrodes (8 × 8 mm; 0.5 mm thick) (Figure 1). The gap between the preparation and the electrodes was wide enough to allow undisturbed contractions, and yet sufficiently narrow to permit effective stimulation of intramural nerve terminals. The preparations were stimulated transmurally by a train of 2-ms square pulses of supramaximal intensity at frequencies of 1, 2, 4, 8, 16, or 32 Hz, 9 V (6), provided by a direct current power supply and a switching transistor triggered by a stimulator (Nihon Kohden, SEN-3201). The responses of the vessel preparations to transmural nerve stimulation were measured for a long enough time to assure equilibrium responses.

Enflurane Delivery

Concentration-response curves to norepinephrine, phenylephrine, and tyramine were determined by the method of stepwise cumulative addition of the agonist to the bathing media in the presence or

absence of enflurane. Enflurane was delivered from a vaporizer (Cyprane, Enfluratec) in the O2-CO2 mixture aerating the bathing media. The concentration in the resulting gas mixture was monitored continuously by an anesthetic gas monitor (WTI, AG101) calibrated daily with an enflurane mixture. To determine the time of equilibration of enflurane, the concentration of enflurane in bathing media was measured by gas chromatography (Shimazu, GC-9A) (7). It was found that equilibration of the bathing solution with enflurane was complete within 30 min and that stable bath concentrations were achieved at an enflurane-O2-CO2 mixture flow rate of 300 mL/min of gas flow through the fritted glass disk at the bottom of the bath chamber. Therefore, after a 30-min equilibration period, the experiments were carried out. The bath anesthetic concentrations after a 30-min equilibration were 6.40 ± 0.84 , 12.98 ± 1.04 , and $18.72 \pm$ 1.58 mg/100 mL (mean \pm sem, n = 3). These concentrations are equivalent to 1 (1.68 vol%), 2 (3.36 vol%), and 3 MAC (5.04 vol%) multiples in humans, respectively.

Drugs

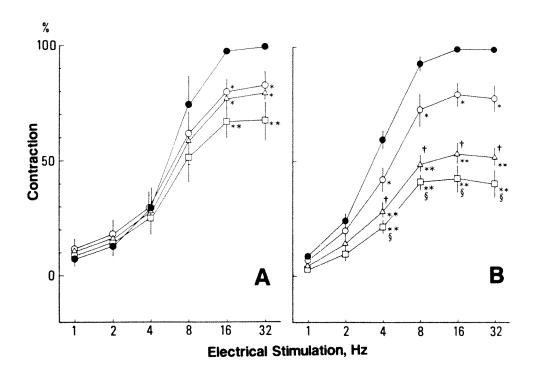
The following drugs were used: enflurane (Abbott, North Chicago, Ill.), *dl*-norepinephrine hydrochloride (Sigma, St. Louis, Mo.), *l*-phenylephrine hydrochloride (Wako Pure Chemical, Tokyo, Japan), and tyramine hydrochloride (Wako Pure Chemical). All these drugs except enflurane were dissolved in pure water and diluted in the Krebs' solution gassed with a mixture of 95% O₂–5% CO₂ before being added to the organ chamber.

Analysis of Data

All data are expressed on the basis of arterial and vein weights of 8 and 10 mg, respectively, to correct for variations in tissue weight. The mean (\pm ' SEM) weights of tissues were 7.53 \pm 4.34 (artery) and 9.40 \pm 1.50 mg (vein) (n=9–21). Two sets of statistical comparisons were made. Student's t-test for paired samples was used when comparing two populations to each other. Comparisons of subsequent interventions to controls were made using a one-way analysis of variance, followed by a Duncan's multiple range test (8). Differences were considered significant when P < 0.05.

Results

Transmural electrical stimulation (1–32 Hz) produced contractile responses of the vessel preparations; the



responses to 16 and 32 Hz in arteries (Figure 2A) and to 4–32 Hz in veins (Figure 2B) were attenuated by exposure to 1–3 MAC enflurane. It should be noted that enflurane elicited a concentration-dependent attenuation in vein preparations.

Having suggested the possibility that enflurane inhibits norepinephrine release from sympathetic nerve endings in the vessel wall, we next turned to the effect of enflurane on the concentration-response curves for exogenously added norepinephrine, a mixed α_1 - and α_2 -adrenoceptor agonist (9), and phenylephrine, a selective α_1 -adrenoceptor agonist (10) in mesenteric arteries and veins. Norepinephrine and phenylephrine produced maximal responses of about the same magnitude; however, norepinephrine was more potent than phenylephrine (Figure 3). This would appear to fit with the data of Guimaraes and Paiva (11). Enflurane at 1 MAC had no significant effect on the concentration-response curves of the arteries and veins to norepinephrine, whereas at the higher concentrations used (2 and 3 MAC) norepinephrine-evoked contraction of the vessels was attenuated (Figure 4). In veins, furthermore, the contractile effect of norepinephrine in concentrations ranging between 10^{-15} and 10^{-4} M was attenuated by exposure to enflurane, in a concentration-dependent manner (Figure 4B). The depression of contraction caused by enflurane on the concentration-response curves of norepinephrine and phenylephrine was more marked with phenylephrine than with norepinephrine (Figures 4 and 5); enflurane (1-3 MAC)

Figure 2. Effect of enflurane (\bullet , 0 MAC; \bigcirc , 1 MAC; \triangle , 2 MAC; \square , 3 MAC) on responses of mesenteric arteries (**A**) and veins (**B**) to transmural nerve stimulation. Responses to 32-Hz stimulation without enflurane in the arteries (2.29 \pm 0.21 g) and the veins (2.63 \pm 0.33 g) are taken as the maximum, and other data are plotted as percentages of it. The *points* represent the mean (n=6–7) and vertical lines show SEM. ***Significantly (*P < 0.05; **P < 0.01) different from the corresponding value without enflurane. †Significantly (P < 0.01) different from the corresponding value for 1 MAC enflurane. Significantly (P < 0.05) different from the corresponding value for 2 MAC enflurane.

caused a concentration-dependent attenuation of the responses evoked by 10^{-5} to 10^{-3} M phenylephrine (Figure 5). These results are consistent with the idea that enflurane attenuates the contractile responses of the vessels to norepinephrine and phenylephrine probably by interfering with postjunctional α_1 -receptor function.

To describe further the effect of enflurane, concentration-response curves of the arteries and the veins were determined for tyramine in the presence and absence of enflurane. The results of the experiments are shown in Figure 6. Tyramine caused a concentration-dependent contraction in the arteries or the veins. The maximum contraction was attenuated by 1–3 MAC of enflurane in mesenteric veins but only by 3 MAC of enflurane in the arteries.

Discussion

Although administration of certain volatile anesthetics in animals and humans may not always result in

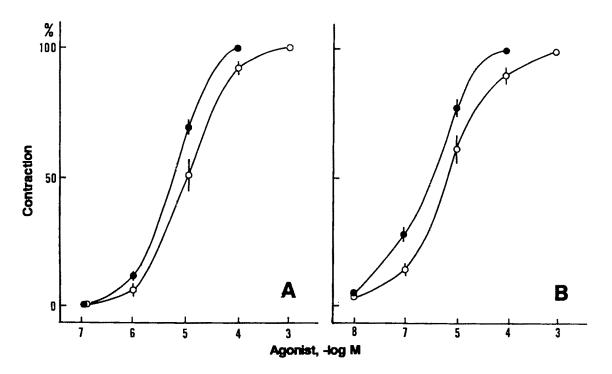
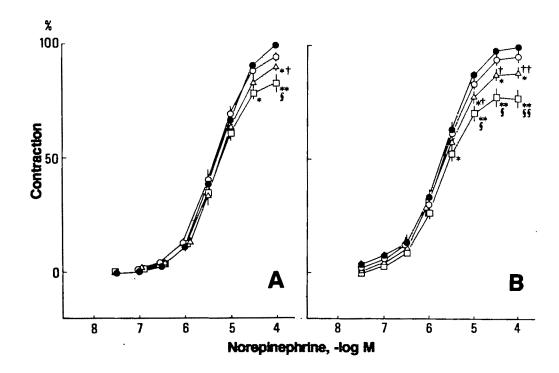


Figure 3. Above. Concentration-response curves to norepinephrine (\bullet) and phenylephrine (\bigcirc) in the arteries (A) and veins (B). Responses to 10^{-4} M norepinephrine (arteries, 2.96 ± 0.13 g; veins, 3.18 ± 0.23 g) and 10^{-3} M phenylephrine (arteries, 3.00 ± 0.41 g; veins, 2.92 ± 0.22 g) are taken as 100%, and other data are plotted in relation to it. Maximum responses to norepinephrine and phenylephrine were not significantly different in any preparation. The points represent the mean (n = 10–18), and vertical lines show SEM.

Figure 4. Below. Modification by enflurane (ullet, 0 MAC; \bigcirc , 1 MAC; \triangle , 2 MAC; \square , 3 MAC) of the contractile response to norepinephrine in mesenteric arteries (A) and veins (B). Contractions induced by 10^{-4} M norepinephrine without enflurane in the arteries (2.85 \pm 0.14 g) and the veins (2.94 \pm 0.21 g) are taken as 100%, and other data are plotted in relation to it. The points represent the mean (n=11) and vertical lines show SEM. ***Significantly (*P<0.05; **P<0.01) different from the corresponding value without enflurane. †,††Significantly (†P<0.05; ††P<0.01) different from the corresponding value for 1 MAC enflurane. *\$\frac{5}{5}\$Significantly (P<0.05; *P<0.05) different from the corresponding value for 2 MAC enflurane.



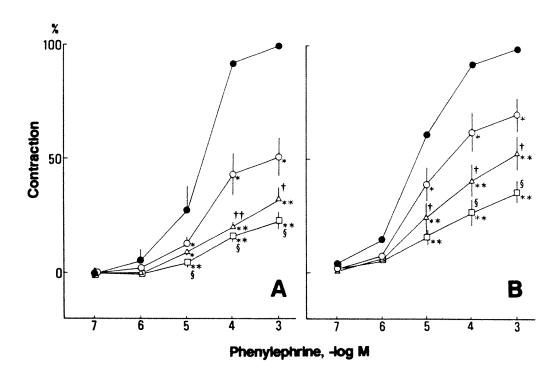
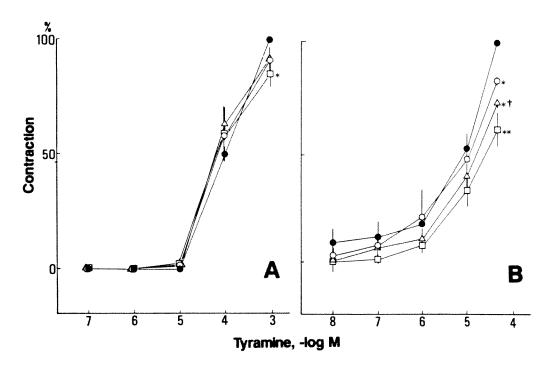


Figure 5. Above. Modification by enflurane (\bullet , 0 MAC; \bigcirc , 1 MAC; \triangle , 2 MAC; \square , 3 MAC) of the contractile response to phenylephrine in mesenteric arteries (**A**) and veins (**B**). Contractions induced by 10^{-3} M phenylephrine without enflurane in the arteries (2.43 \pm 0.32 g) and the veins (2.64 \pm 0.32 g) are taken as 100%, and other data are plotted in relation to it. The *points* represent the mean (n=5) and *vertical lines* show SEM. ***Significantly (*P<0.05; **P<0.01) different from the corresponding value without enflurane. †,††Significantly (†P<0.05; ††P<0.01) different from the corresponding value for 1 MAC enflurane. *Significantly (P<0.05) different from the corresponding value for 3 MAC enflurane.

Figure 6. Below. Modification by enflurane (ullet, 0 MAC; \bigcirc , 1 MAC; \triangle , 2 MAC; \square , 3 MAC) of the contractile response to tyramine in mesenteric arteries ($\bf A$) and veins ($\bf B$). Contractions induced by 10^{-4} M tyramine without enflurane in the arteries (2.28 ± 0.27 g) and the veins (2.24 ± 0.23 g) are taken as 100%, and other data are plotted in relation to it. The *points* represent the mean (n=4-5) and *vertical lines* show SEM. ***Significantly (*P < 0.05; **P < 0.01) different from the corresponding value without enflurane. †Significantly (P < 0.05) different from the corresponding value for 1 MAC enflurane.



peripheral vasodilatation, it is agreed that deep (surgical) anesthesia, when induced by these agents, will result in dilatation and hypotension (12,13). Up until recently, it was thought that such anesthetic-induced vasodilatation was due exclusively to effects of these anesthetics on the central (14) and autonomic nervous systems (15) and on the myocardium (16,17), and that concentrations of anesthetics used to induce surgical anesthesia could exert direct depressant and vasodilator effects on vascular smooth muscle (18–20).

The response of the vascular smooth muscle to transmural nerve stimulation is due to release of norepinephrine from adrenergic nerves innervating the blood vessels as evidenced by the attenuation produced by the adrenergic neuronal blocking agents bretylium and guanethidine, the neuronal blocking agent tetrodotoxin, the α -receptor-blocking agents phentolamine and tolazoline, and by the enhancement produced by the uptake₁-blocking agent cocaine, and, in the presence of blockade of uptake₁, by the uptake₂-blocking agent hydrocortisone (6,21–24). The present study demonstrates that enflurane appears to be able to (a) inhibit the release of endogenous norepinephrine from sympathetic nerve endings and (b) depress contractile response to norepinephrine by interfering with postjunctional α_1 -adrenoceptor function. These postulates are inferred from the following observations: (a) the contractile responses of mesenteric arteries and veins to transmural nerve stimulation and norepinephrine are reduced by enflurane (Figures 2 and 4) and (b) enflurane reduces the responses to phenylephrine more than those to norepinephrine (Figures 4 and 5). This differential inhibition by enflurane may be a consequence of its preferential interference with α_1 adrenoceptors, on the one hand, and to the relatively higher affinity of phenylephrine for α_1 - compared with α_2 -adrenoceptors (25), on the other. It is well known that norepinephrine is a mixed α_1/α_2 adrenoceptor agonist, whereas phenylephrine is a relatively selective α_1 -adrenoceptor agonist. The ratio between EC₅₀ values for α_2 - and α_1 -adrenoceptormediated responses in the rabbit pulmonary artery, for example, is 0.6 for norepinephrine and 31 for phenylephrine (9). This means that only at high concentrations (close to those required for maximal responses) does phenylephrine activate α_2 -adrenoceptors (26). This may explain why enflurane, at all concentrations used (1-3 MAC), reduced the responses to phenylephrine more than responses to norepinephrine. Interpretation of our experimental data that contractile effect of norepinephrine is more potent than that of phenylephrine (Figure 3) implies

that norepinephrine is able to activate both α_1 - and α_2 -adrenoceptors with similar efficacy (26).

It is known that tyramine depolarizes the smooth muscle membrane by direct and indirect actions in dog mesenteric artery (27) and in rabbit ear artery (28); the indirect action is mediated by release of neuronal norepinephrine, which acts on α_1 -adrenoceptors. Furthermore, Miyahara and Suzuki (28) found that transmural nerve stimulation releases norepinephrine from the guanethidine-sensitive norepinephrine compartment but not from the tyraminesensitive compartment found in adrenergic nerve endings. If the view that enflurane can inhibit release of norepinephrine associated with electrical stimulation-induced nerve-membrane depolarization is correct, when compared with the effect of enflurane on transmural nerve stimulation-induced responses, exposure of tissues to enflurane would result in slight attenuation of the responses to tyramine, presumably only by interfering with an interaction between released norepinephrine and postjunctional α_1 adrenoceptors, but not by inhibition of norepinephrine release from tyramine-sensitive compartment in sympathetic nerve endings. Indeed, in contrast to the results with transmural nerve stimulation (Figure 2), the responses caused by tyramine were less sensitive to enflurane inhibition (Figure 6). The refractoriness to enflurane observed when contractions of mesenteric arteries and veins were caused by tyramine, but not by transmural nerve stimulation, might be due to the absence of some specific enflurane-sensitive action site in the process that leads to inhibition of tyramine-induced release of norepinephrine.

It is assumed that venous smooth muscle cells, in general, are more sensitive to the inhibitory actions of anesthetics than are arterial smooth muscle cells (29,30). In the present experiments, the effect of enflurane on contractile responses to transmural nerve stimulation and to exogenously added norepinephrine was more evident in veins than in arteries; also, the effects of enflurane on responses of arteries and veins to phenylephrine are the same, thus suggesting that venous responses to sympathetic nerve activation are susceptible to enflurane.

Clearly, further work is required to elucidate the exact influence of enflurane in the molecular and biochemical reaction sequence leading to alterations in cardiovascular system. It is already clear, however, that enflurane acts on sympathetic nerve endings to inhibit release of norepinephrine associated with nerve-membrane depolarization, and that enflurane may interfere with postjunctional α_1 -adrenoceptors in the vascular smooth muscle of mesenteric arteries and veins.

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A Comparison of Labetalol and Nitroprusside for Inducing Hypotension During Major Surgery

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GOLDBERG ME, McNULTY SE, AZAD SS, CANTILLO J, TORJMAN M, MARR AT, HUFFNAGLE S, SELTZER JL. A comparison of labetalol and nitroprusside for inducing hypotension during major surgery. Anesth Analg 1990;70:537–42.

The hemodynamic and intrapulmonary shunt effects of intravenous labetalol and nitroprusside were compared during induced hypotension for major spinal surgery. A randomized, double-blind protocol was used in which 20 patients, ASA physical status I or II, received either nitroprusside infusion (n=10) or labetalol bolus injections of 10 mg every 10 min (n=10) until mean arterial blood pressure was reduced to 55–60 mm Hg. Pulmonary artery pressures were measured and mixed venous samples obtained via a pulmonary artery catheter. Nitroprusside increased heart rate significantly more than labetalol during the period of hypotension. When compared with prehypotension baseline values, nitroprusside increased heart rate

significantly with a concomitant significant decrease in systemic vascular resistance. Cardiac output increased significantly 60 min after hypotension was achieved in patients treated with nitroprusside. Systemic vascular resistance decreased significantly below baseline levels in patients treated with labetalol but without changes in cardiac output, heart rate, or mean pulmonary artery pressure. There was a 122% increase in intrapulmonary shunt with nitroprusside administration, compared with an 11% increase with labetalol. Labetalol was effective for inducing hypotension and was not associated with an increase in heart rate, intrapulmonary shunt, or cardiac output as seen with nitroprusside.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—labetalol, nitroprusside. PHARMACOLOGY, NITROPRUSSIDE. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—labetalol.

Induced hypotension has been used to facilitate various surgical procedures (1) and to reduce the need for blood transfusion. Sodium nitroprusside is the drug most commonly used for this purpose (2). As nitroprusside is not devoid of adverse effects such as tachycardia, tachyphylaxis, increased intrapulmonary shunt (3), and cyanide toxicity (4), the search for other useful agents has continued. Labetalol, an α -and β -adrenergic blocking agent, in combination with various inhalation anesthetics, has been advocated for the induction of hypotension (5–9). Although it has been suggested that labetalol, when used to

produce deliberate hypotension, may not increase intrapulmonary shunting, there is insufficient evidence to support this. The purpose of this study was to compare the intrapulmonary shunt effects as well as the hemodynamic changes of labetalol and nitroprusside when used to induce hypotension during general anesthesia for major surgery on the spine.

Methods

Twenty patients, ASA physical status I or II, undergoing major orthopedic spinal procedures gave their informed consent to participate in this protocol, which had been approved by our institutional review board. Patients were excluded from the study if they had a history of myocardial infarction in the last 6 mo, congestive heart failure, hypertension (blood pressure above 140/95 mm Hg), bradycardia (<55 beats/min), heart block greater than first degree, or chronic

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obstructive pulmonary disease. Monitoring included an indwelling radial artery catheter, a pulmonary artery catheter, and a processed two-channel electroencephalogram (Lifescan, Diatek, Inc., San Diego, Calif.). Anesthetic technique consisted of premedication with 0.08 mg/kg morphine and 0.4 mg atropine sulfate intramuscularly. Induction was performed using 4-6 mg/kg intravenous thiopental and 3-5 μg/kg fentanyl. Tracheal intubation was facilitated with 1 mg/kg intravenous succinylcholine. Anesthetic maintenance consisted of 60%-70% nitrous oxide in oxygen and isoflurane at an end-tidal concentration of 0.6%-0.7% monitored with a Datex 254 (Puritan-Bennett Corporation, Helsinki, Finland) end-tidal gas monitor. Muscle relaxation was maintained with 0.05 mg/kg vecuronium. Ventilation was controlled to maintain the Paco₂ between 32 and 38 mm Hg and adjusted according to repeated blood gas measurements. Blood loss was determined by measuring the weights of the sponges and by measuring the volume of blood in suction-trap bottles. Three milliliters of Plasmalyte was infused for each milliliter of blood lost until the calculated "allowable blood loss" was reached. Allowable blood loss was based on the following formula: $V_L = EBV \times (H_o - H_F/HAV)$, where V_L = allowable blood loss, EBV = patients' estimated blood volume (65 mL/kg), H_o = preoperative hematocrit, H_F = minimal allowable hematocrit (27%), and HAV = the average of the initial and minimal allowable hematocrit (10). Blood loss beyond the allowable level was replaced with an equivalent volume of transfused blood (autologous whole blood or packed red blood cells).

At the start of laminectomy, hypotension was induced with either a nitroprusside infusion (n = 10) or labetalol bolus injection(s) (n = 10). Drug selection was assigned randomly, with a computer-generated random table. Nitroprusside was prepared as a 0.02% solution; infusion was initiated at 0.2 μg·kg⁻¹·min⁻¹ and increased every 10 min by 0.2 μ g·kg⁻¹·min⁻¹ until either mean arterial blood pressure (MAP) was reduced to 55-60 mm Hg or a dose of 10 $\mu g \cdot k g^{-1} \cdot min^{-1}$ was given. Labetalol was administered in 10-mg increments every 10 min until either MAP was 55-60 mm Hg or 300 mg had been given. Patients exceeding drug dosage limits were eliminated from the study, and additional therapy was instituted at the discretion of the attending anesthesiologist. Each patient received both an infusion and bolus injections, with the active drug being administered via one route and saline via the other. Heart rate (HR), MAP, central venous pressure, and pulmonary artery systolic and diastolic pressures, as well as temperature and ETco2 were monitored throughout the study. Pulmonary artery occlusion pressure was measured at end expiration, and cardiac output (CO) was measured using the thermodilution technique. Hemodynamic variables were recorded before induction of anesthesia (preinduction); immediately before induction of hypotension; when the desired level of hypotension was achieved; every 15 min thereafter; at the termination of the administration of nitroprusside or labetalol; and every 15 min until MAP returned to baseline values. Systemic vascular resistance (SVR) and pulmonary vascular resistance were calculated using standard formulas.

Arterial and mixed venous gas tensions were also measured at each of the above times to determine right-to-left shunt fractions. Arterial and mixed venous blood gas samples were collected anaerobically in plastic preheparinized syringes and iced immediately before being analyzed within 10 min on a Radiometer ABL 330 (Radiometer America, Cleveland, Ohio) blood gas analyzer calibrated using the manufacturer's aqueous buffer and external controls before each case. Blood gas tensions were corrected for body temperature. Alveolar oxygen tension (Pao₂) was calculated using the formula

$$PaO_2 = (P_B - PH_2O)(FIO_2) - \frac{PaCO_2}{R},$$

where Fio₂ represents the fraction of inspired oxygen, Paco₂ the arterial carbon dioxide partial pressure, P_B the barometric pressure, and R the respiratory quotient. We assumed an R value of 0.8 before induction of anesthesia while the patient was breathing room air and one of 1.0 after induction of anesthesia. Water vapor pressure (PH₂O) was corrected for temperature (9). A standard shunt formula was used for calculating the shunt fraction, one that includes the V/Q contribution as well as true shunt:

$$\frac{\mathrm{Qs}}{\mathrm{Qt}} = \frac{\mathrm{Cco}_2 - \mathrm{Cao}_2}{\mathrm{Cco}_2 - \mathrm{Cvo}_2} \times 100,$$

where Qs/Qt represents shunt fraction, Cco_2 the capillary oxygen content obtained from the alveolar air equation, Cao_2 the arterial oxygen content calculated using $(1.35 \times \text{Hgb} \times \% \text{ saturation}) + 0.003 \times \text{Pao}_2$ and Cvo_2 the mixed venous oxygen content calculated in a way similar to that used for Cao_2 , using mixed venous partial pressure obtained from the pulmonary artery catheter. Shunt values were not calculated preinduction because of inconsistency of the Fio_2 . Intergroup and intragroup comparisons were made utilizing analysis of variance with repeated measures and matrix cell contrast, where applicable. A P value of <0.05 was considered statis-

Table 1. Demographics

	Male/ Age female (yr)		Height (cm)	Weight (kg)	
Labetalol	6/4	45.5 ± 9.2	175.0 ± 9.6	83 ± 14.6	
Nitroprusside	8/2	41 ± 13.1	178.3 ± 11.7	89.1 ± 22	

Age, height, and weight are expressed as mean ± sp.

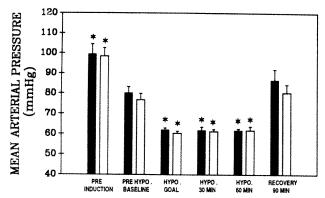
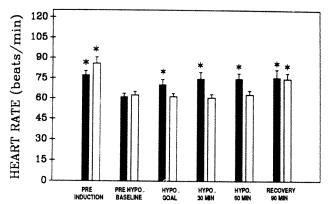


Figure 1. Mean \pm sem arterial pressure at each time period. Hypo = systemic arterial hypotension; Pre Induction = before induction of anesthesia; Pre Hypo. Baseline = immediately before induction of hypotension; Hypo. Goal = when desired level of hypotension was achieved; Recovery 90 min = 90 min after stopping drug given to lower blood pressure. Filled column, nitroprusside (n=9); open column, labetalol (n=9). *P<0.05 vs baseline prehypotension.

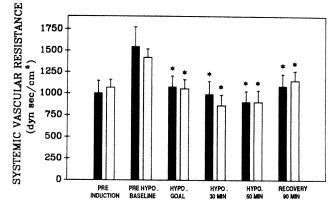
tically significant. Values are reported as mean \pm SEM unless indicated otherwise.

Results

Data from two patients have been deleted (one given nitroprusside, the other labetalol) because of technical problems. No patients were eliminated from the study as a result of their having exceeded the drugdose limitations mentioned above. There were no significant differences in demographics (age, height, weight) and preinduction hemodynamic or blood gas tension values between the two groups (Table 1). Hypotension was easily achieved with both drugs (Figure 1). The time to obtain goal blood pressure took longer with nitroprusside (55.3 \pm 45 min) than with labetalol (21.25 \pm 13.4 min). This is explained by the slow titration schedule used for nitroprusside in order to avoid undue hypotension. The duration of hypotension was not significantly different between the two groups (labetalol 223 ± 175 min, nitroprusside 140 ± 44 min). When labetalol administration over time was examined (i.e., hours 1-5 of induced hypotension), mean doses were larger in the first hour but then stabilized over hours 2-5. The mean doses of labetalol per hour for the first 5 h were 28.5,



<u>Figure 2</u>. Mean \pm SEM HRs at each time period. Filled column, nitroprusside (n = 9); open column, labetalol (n = 9). *P < 0.05 vs baseline prehypotension. (See Figure 1 for abbreviations.)



<u>Figure 3</u>. Mean \pm sem SVR at each time period. *Filled column*, nitroprusside (n = 9); open column, labetalol (n = 9). *P < 0.05 vs baseline prehypotension. (See Figure 1 for abbreviations.)

15.0, 17.5, 16.7, and 20 mg. For nitroprusside these values were 2.3, 4.3, 5.0, 4.6, and 1.3 mg for hours 1–5, respectively.

When the hemodynamic values were compared between the two groups, no significant differences were seen in MAP, pulmonary artery occlusion pressure, SVR, pulmonary vascular resistance, central venous pressure, or Qs/Qt at any of the testing times. Nitroprusside significantly increased HR during hypotension, whereas labetalol produced no significant change in HR from baseline levels. There were no other significant intergroup differences.

When the hemodynamic variables were compared within each group with the baseline (prehypotension) values, there was a significant increase in HR (Figure 2) accompanied by a significant decrease in SVR (Figure 3) in the nitroprusside group. Cardiac output, in the nitroprusside group, did not change during the initial period of hypotension but increased significantly 60 min (Figure 4) after hypotension was achieved. Mean pulmonary artery pressures did not change significantly in either group. Labetalol did not

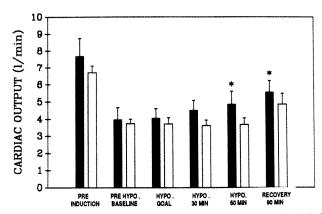


Figure 4. Mean \pm SEM CO values at each time period. Filled column, nitroprusside (n = 9); open column, labetalol (n = 9). *P < 0.05 vs baseline prehypotension. (See Figure 1 for abbreviations.)

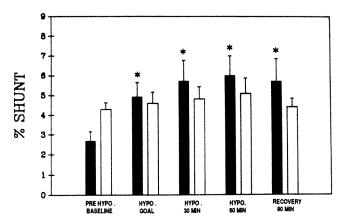


Figure 5. Intraoperative right-to-left shunt at each time period (mean \pm sem). Filled column, nitroprusside; open column, labetalol. *P < 0.05 vs baseline prehypotension. (See Figure 1 for abbreviations.)

significantly change HR (Figure 2), CO (Figure 4), or pulmonary artery pressure from baseline levels. Systemic vascular resistance decreased significantly in the labetalol group (Figure 3). No significant difference was seen in blood loss or the reduction in hemoglobin concentration between the two groups. The time required for MAP to return to baseline prehypotension values was significantly shorter with nitroprusside (20.72 \pm 20.13 min) than with labetalol (43.12 \pm 21.70 min).

Intrapulmonary shunts were similar in the two groups before induction of hypotension. We were unable to measure intrapulmonary shunting preinduction accurately because of a variable patient Fio₂ after pulmonary artery catheter placement. With the induction of hypotension, there was an 81.5% increase in shunt fraction in the nitroprusside group as compared with a 7% increase in the labetalol group (Figure 5). Subsequently, shunt fraction continued to

increase and was 122% greater than baseline values at 60 min into the hypotension period in the nitroprusside group (Table 2). The labetalol group showed no significant increase in shunt, and there were no significant changes in pulmonary vascular resistance.

Discussion

In this prospective, randomized, double-blind study, hypotension was easily achieved with administration of labetalol or nitroprusside. In the nitroprusside group, hypotension was achieved by a decrease in SVR but at the cost of an increased HR with subsequent increase in CO. Although HR increased significantly after nitroprusside administration, the HR did not increase above preinduction values. In the labetalol group, the decrease in SVR was not accompanied by a change in HR, and CO was maintained at baseline values. The observed hemodynamic effects of labetalol probably result from the combined α - and β -adrenergic receptor blocking activity (11,12).

Labetalol has been used to induce hypotension in combination with inhalation anesthetics during various surgical procedures. Fairbairn and associates (6) compared isoflurane and halothane in combination with labetalol for induced hypotension during middle-ear microsurgery. Labetalol was given to all patients in increments of 10 mg to decrease systolic pressure to 70 mm Hg. Hypotension was achieved with a mean dose of 52 mg in the halothane group and 60 mg in the isoflurane group, which demonstrated that labetalol was equally effective with both anesthetics. In addition, McNulty and colleagues (7) demonstrated that labetalol given in 10-mg increments every 5-10 min allowed a satisfactory reduction in MAP to 55-60 mm Hg in patients having orthognathic surgery. These studies did not compare labetalol to other agents nor did they address the full cardiovascular or pulmonary vascular changes occurring with use of labetalol in this fashion.

Fahmy et al. (9), in an earlier unblinded study, demonstrated that both labetalol and nitroprusside were useful for the induction of hypotension. They found that doses of labetalol of 90–230 mg were required to provide hypotension for durations of 3–6 h. In this study, enflurane rather than isoflurane was utilized for maintenance of anesthesia. Our findings (mean total dose of labetalol 29.37 ± 21.94 mg) agree with those of Scott et al. (13) and Kaufman (14) who reported that only small doses of labetalol are necessary to achieve hypotension. The results of the present study show that the time for recovery to prehypotension blood pressure was longer with labe-

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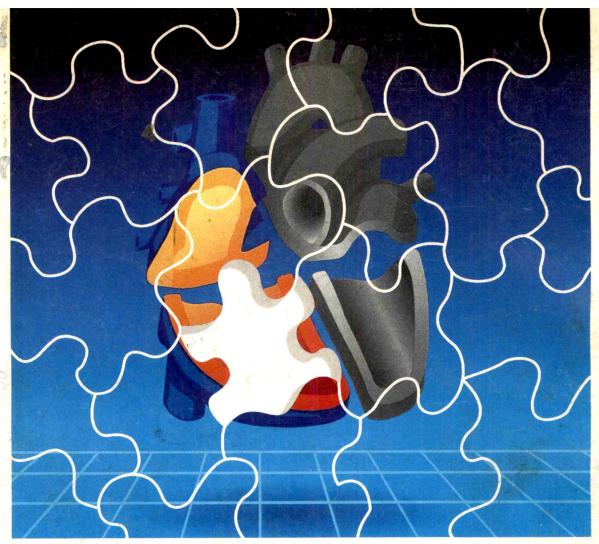
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Table 2. Intrapulmonary Qs/Qt During Induced Hypotension With Labetalol and Nitroprusside

	Prehypo baseline	Hypo/goal	30 min hypo	60 min hypo	60 min posthypo/recovery
% Shunt (Qs/Qt)					
N	2.7 ± 1.2	4.9 ± 1.8	5.7 ± 2.7	6.0 ± 2.6	5.7 ± 3.0
L	4.3 ± 0.9	4.6 ± 1.6	4.8 ± 1.7	5.1 ± 2.2	4.4 ± 1.2

Prehypo baseline = immediately before induction of hypotension; hypo/goal = when the desired level of hypotension was achieved; 30 min hypo = 30 min after hypo/goal; 60 min hypo = 60 min after hypo/goal; 60 min hypo = 60

No significant differences between labetalol (L) and nitroprusside (N) groups. All shunt fractions are expressed as mean percent ± SEM.

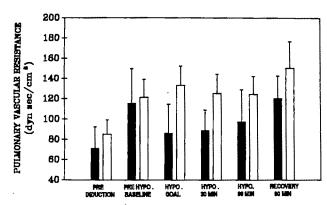


Figure 6. Mean \pm sem pulmonary vascular resistance at each time period. Filled column, nitroprusside (n = 9); open column, labetalol (n = 9). (See Figure 1 for abbreviations.)

talol (43.12 \pm 21.70 min) than with nitroprusside (20.72 \pm 20.13 min). This might be of concern if a rapid return to normal blood pressure were needed. This difference, although important, is not unexpected, as labetalol has a longer elimination half-life than nitroprusside (15). In the event that ischemia or electroencephalographic changes were noted due to an uncontrolled decrease in blood pressure, rapid reversal of hypotension would be indicated and could be achieved with ephedrine or epinephrine.

The shunt fractions in our study were generally similar to those reported by others in anesthetized individuals in the absence of hypotension (16,17), although lower values were seen in the labetalol and nitroprusside baseline groups. We speculate that our lower baseline shunt values are attributable to the fact that our data were obtained with the patients in the prone position, a position known to improve ventilation/perfusion matching (17). Several authors have shown that induced hypotension with nitroprusside increases intrapulmonary shunting (3,18). Casthely and colleagues (18), for example, found that the increase in shunt might be sufficient to affect pulmonary gas exchange adversely in patients without lung disease. They suggested that this increase in shunt may be secondary to inhibition of hypoxic pulmonary vasoconstriction by nitroprusside. In a similar fashion, we found that nitroprusside significantly increased shunt fraction under the conditions set forth

in this study. This increase did not occur with labetalol. It should also be noted that pulmonary vascular resistance values in the sodium nitroprusside group showed a decrease from baseline prehypotension, as illustrated in Figure 6, but this did not reach statistical significance. In our patients the increase in shunt fraction occurring with nitroprusside did not result in hypoxemia or in a significant decrease in oxygen delivery. However, in a more compromised patient, these changes could be more pronounced, thereby conferring a clinical advantage on the use of labetalol in place of nitroprusside for the controlled reduction of blood pressure.

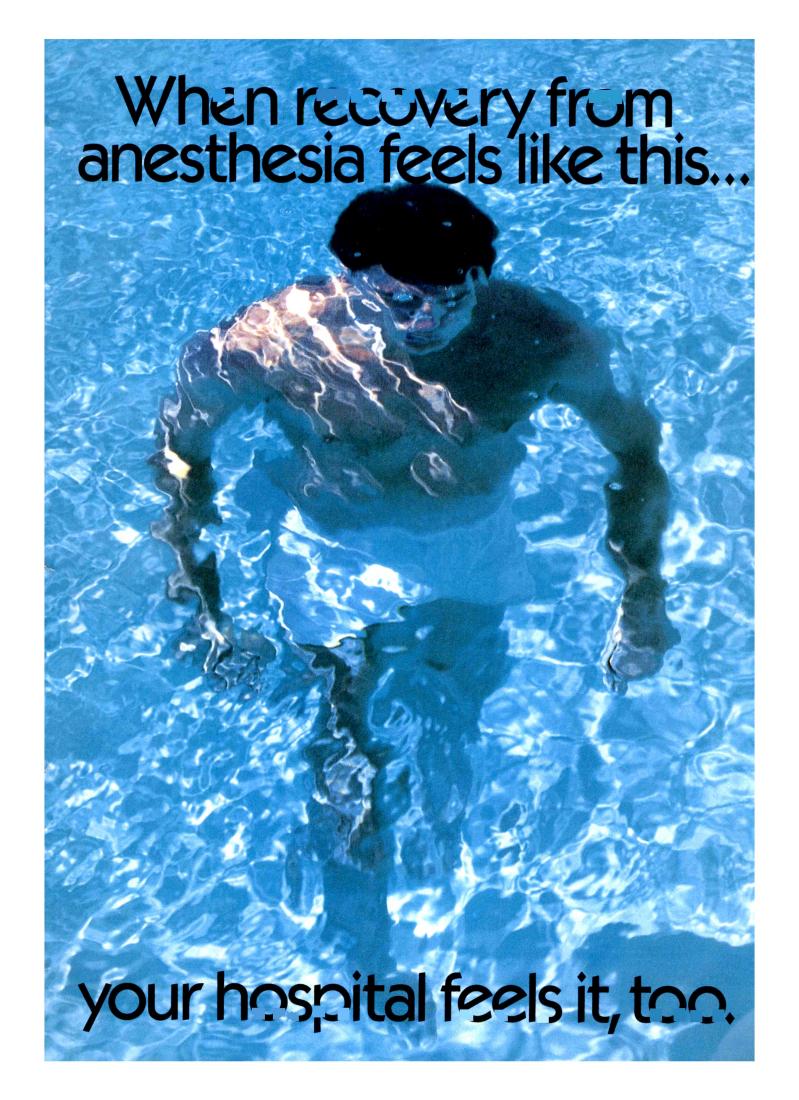
Labetalol and nitroprusside administered with low-dose isoflurane are useful agents for inducing hypotension. Labetalol, however, produced only minimal increases in intrapulmonary shunting with no increase in HR or CO, whereas significant increases in both HR and shunt fraction were seen with nitroprusside.

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- temic hemodynamics and arterial oxygenation. Anesth Analg 1988;67:S58.
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New IV anesthetic agent

DIPRIVAN

INJECTION 10 mg/mL propofol



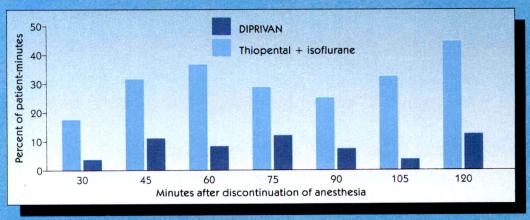
Used for induction and maintenance, DIPRIVAN offers patients a rapid,¹ alert emergence from anesthesia—with less of the nausea and vomiting associated with thiopental/isoflurane anesthesia.²⁻⁵

Significantly faster speed of recovery than with thiopental/isoflurane⁵

	DIPRIVAN (n = 20)	Thiopental/isoflurane (n = 20)
Mean duration of postanesthesia recovery Phase I*	21.0 min [†]	37.5 min
Mean time until suitable for discharge	95.5 min [†]	118.9 min

^{*}From end of anesthesia to time when Aldrete score of 10 was first recorded. $\dagger P < 0.01$, statistically significant differences with DIPRIVAN (based on parametric and nonparametric estimates of the distribution of recovery times).

Significantly lower incidence[‡] of nausea, retching, and vomiting than with thiopental/isoflurane⁵



[‡]Height of a column represents the percentage of affected patient-minutes among *all* the patient-minutes recorded during a given 15-minute increment. The overall incidence of adverse events is substantially reduced with DIPRIVAN compared with thiopental + isoflurane (P < 0.01).

The first of a new class of IV anesthetic agents for induction and maintenance

DIPRIVAN, an alkylphenol, provides:

Rapid, predictable onset

 smooth induction with minimal excitation (one arm-brain circulation)

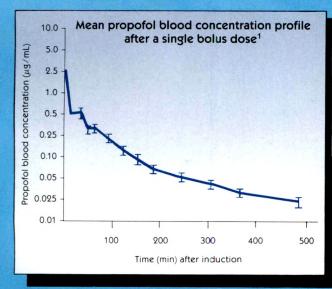
Rapid metabolism and extensive distribution*

- total body clearance exceeds estimates of hepatic blood flow¹
- no active metabolites

Rapid, clearheaded awakening

- majority of patients are generally awake, responsive, and oriented within 8 minutes
- low incidence of nausea and vomiting²

*As with most anesthetic agents, the clearance rate of DIPRIVAN decreases in elderly patients.



DIPRIVAN clearance 5-10 times faster than barbiturates				
Clearance rate (L/min) [†]				
DIPRIVAN	1.6-3.4			
thiopental ³	.1130			
methohexital ³	.7084			

'Calculations of clearance rates based on 70-kg patient -adapted from Way and Trevor, p 803³ New awakening in anesthesiology...

DIPRIVAN® proposol

Alert emergence

Significantly faster recovery profile

Awakening was faster with DIPRIVAN than with thiopental/isoflurane...and DIPRIVAN patients were considered suitable for discharge significantly (P < 0.05) sooner.⁴

DIPRIVAN Thiopental/isoflura							
Duration of anesthesia	85*	57					
Response to commands	3.5*	6.1					
Eyes open spontaneously	4.0*	6.3					
Fully oriented	5.5	9.4					
Able to tolerate fluids	61*	130					
Able to stand unassisted	68	87					
Able to walk unassisted	70	96					
Able to void	102*	173					
"Ready" for home	138*	206					

^{*}Statistically significant (P < 0.05). Measurements taken from time of discontinuation of all maintenance anesthesia.

With less of the nausea and vomiting associated with other anesthetic agents—up to 24 hours postop



Superior recovery

Improved speed and quality of recovery compared with thiopental/isoflurane:

more rapid time to extubation⁵
more rapid and clearheaded awakening⁶⁻⁸
lower incidence of nausea and vomiting^{2,7}
patients able to tolerate fluids faster^{2,4}

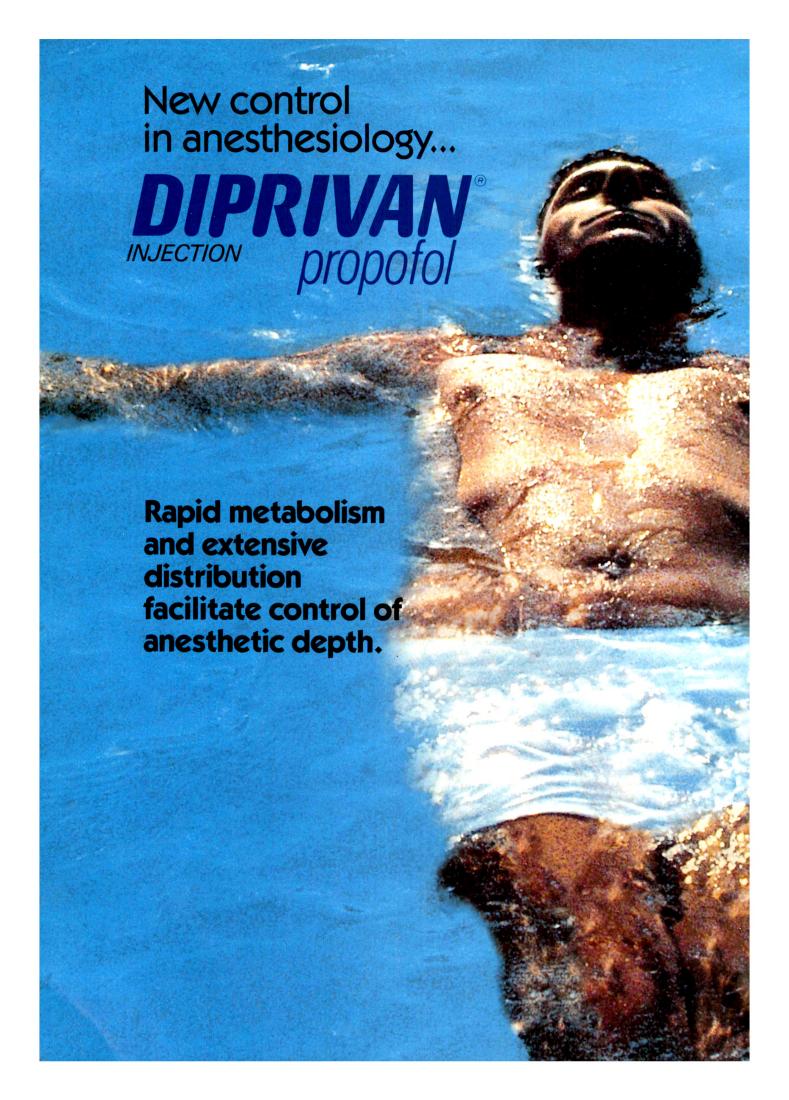
Earlier discharge from PARR*

more efficient utilization of OR/PARR facilities⁹ increased nursing efficiency⁹ rapid return to routine self-care activities

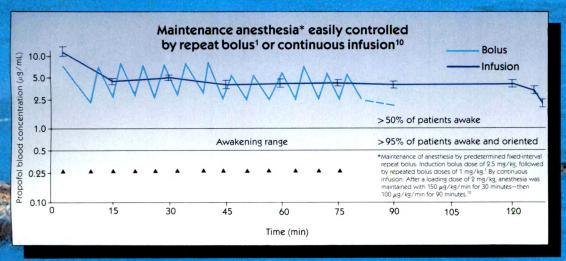
As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

*An adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia.





Maintenance of anesthesia: easily controlled



-adapted from Cockshott, p 48,1 White, p 9,8 and Herregods et al. p 3641

No reported awareness during maintenance with DIPRIVAN

Overall quality of maintenance anesthesia superior to thiopental/ isoflurane.¹¹

Assessment of maintenance*11			
	xcellent	Good	Poor
DIPRIVAN (n = 50)	58%	30%	12%
Thiopental + isoflurane (n = 50)	36%	32%	32%

^{*}Statistically significant differences between all treatment groups (P < 0.05, Mantel-Haenszel Test)—as measured by the percent variation from baseline in hemodynamic parameters.

-adapted from Weingarten and Youngberg, data on file1

When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.



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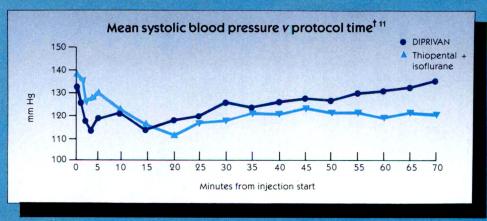
New assurance in anesthesiology...



Worldwide experience in over 7,000,000 patients

Hemodynamic and respiratory effects are dose-dependent

- Hemodynamic effects during induction were generally more pronounced than with traditional IV induction agents.
- Blood pressure predictably decreased on induction (sometimes > 30%) but was within acceptable ranges for healthy individuals.*



-adapted from Weingarten and Youngberg, data on file

¹Induction bolus dose: Patients received either DIPRIVAN 2.5 mg/kg or thiopental 5.0 mg/kg. DIPRIVAN patients were then maintained with repeated injections of 25% of the original induction dose supplemented with 60% to 70% nitrous oxide in oxygen. Thiopental/isoflurane patients were maintained with 0.2% to 2.0% isoflurane supplemented with 60% to 70% nitrous oxide in oxygen.¹¹

* Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

■ Increase in heart rate following intubation was less pronounced than after thiopental with isoflurane. 11,12

■ The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.*

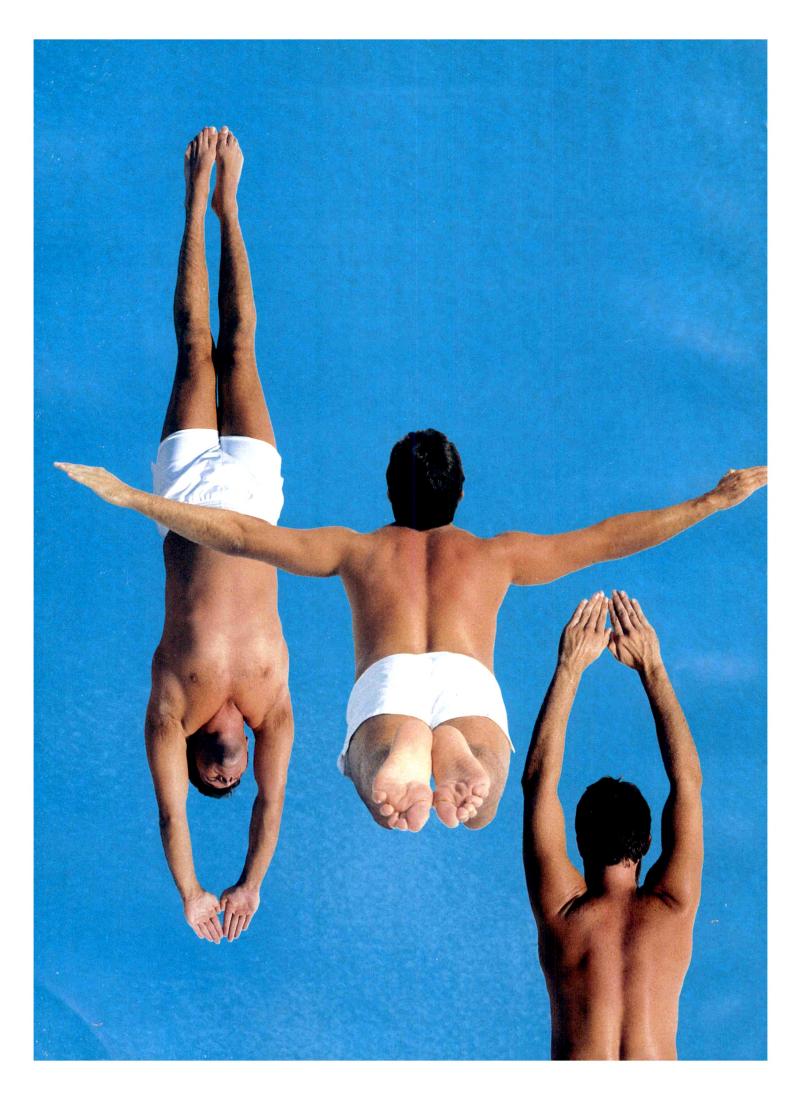
In clinical trials including over 1500 DIPRIVAN patients, most adverse events were mild and transient

- Transient local pain (≥10%) may occur during IV injection; venous sequelae have rarely been reported (<1%).</p>
- Apnea often occurs on induction (43%) and may persist for more than 60 seconds.
- Significant hypotension (5.5%) and bradycardia (2.4%) have been reported[†]; experience has shown them to be clinically manageable.
- Low overall incidence of nausea (16.7%) and vomiting (9.1%).

*Induction dose requirements may be reduced.

[†]Sufficient to require intervention.





New versatility in anesthesiology...



For a wide variety of procedures... outpatient and inpatient

- Gynecologic
- Urologic
- Ophthalmic

- Orthopedic
- Dermatologic
- Diagnostic

■ ENT

■ General surgery

DIPRIVAN should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

DIPRIVAN should be used with caution in elderly, debilitated, and/or hypovolemic patients, and those rated ASA Class III or IV.

DIPRIVAN is not recommended at this time for use in pediatric patients, nursing mothers, patients with increased intracranial pressure or impaired cerebral circulation, and in obstetrics, including cesarean section deliveries.

- DIPRIVAN can be combined with other commonly used agents in anesthesia.
- Also eliminates concerns about operating room/ recovery room pollution associated with volatile agents.

For induction and maintenance...

pharmacokinetic profile

DIPRIVAN

INJECTION 10 mg/mL

The new

propofol IV anesthetic agent with a unique

- for rapid, predictable onset of anesthesia
- for smooth induction with minimal excitation
- for easily controlled maintenance of anesthesia
- for rapid, clearheaded awakening—with a low incidence of nausea and vomiting

Extensive worldwide experience

in a wide variety of surgical procedures outpatient and inpatient

As part of a balanced anesthetic technique, **DIPRIVAN** is a cost-effective alternative to standard induction agents and volatile maintenance agents.

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DIPRIVAŅ INJECTION propofol

EMULSION FOR IV ADMINISTRATIO

C,2H,8O

DESCRIPTION: DIPRIVAN® (propofol) Injection is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-Disopropylphenol and has a molecular weight of 178.27. The empirical and structural formulas are:

Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The emulsion is isotoric and has a pH of 70-85. In addition to the active component, propofol, the formulation also contains soy-bean oil (100 mg/mL), glycerol (22.5 mg/mL) and egg lecithin (12 mg/mL), with sodium hydroxide to adjust pH. CLINICAL PHARMACOLOGY: DIPRIVAN Injection is an intravenous hypnotic agent for use in the induction and maintenance of anesthesia. The pharmacokinetic profile of DIPRIVAN Injection can be characterized as follows: After a single rapid IV bolus dose, two distribution phases are seen, a rapid phase with a half-life of 18 to 8.3. After a single rapid IV bolus dose, two distribution phases are seen, a rapid phase with a half-life of 1.8 to 8 min and a slower phase of 34 to 64 min. These distribution phases are associated with the movement of DIPRIVAN from highly perfused tissues (vessel-rich tissues) to less well-perfused tissues. The terminal elimination half-life may become extended beyond 700 min. With prolonged administration of DIPRIVAN injection, the terminal elimination half-life may become extended beyond 700 min. DIPRIVAN has a high metabolic clearance that ranges from 15 L/min to 3.4 L/min in healthy 70 kg patients. This metabolic clearance exceeds estimates of hepatic blood flow, suggesting possible extrahepatic metabolism. DIPRIVAN has a large steady state distribution volume that ranges from 150 to 1,000 liters in healthy 70 kg patients. The long terminal elimination half-life of DIPRIVAN is due to the large steady state distribution volume which is presumed to be due to extensive drug partitioning

into tissues. The termination of anesthetic drug effects of DIPRIVAN after a single IV bolus or a maintenance infusion is due to extensive redistribution from the CNS to other tissues and high metabolic clearance both of which will decrease blood concentrations. Recovery from anesthesia is rapid. Following induction (2.0 to 2.5 mg/kg/min) of anesthesia for periods up to two hours, the majority of patients are generally awake, responsive to verbal commands, and oriented within 8 minutes. Recovery from the effects of DIPRIVAN Injection occurs due to metabolism and distribution during the first two exponents of the degree cure and in our dependent on the terminal eligination but If it 6. Activity in the chapter sebaged. of the decay curve and is not dependent on the terminal elimination half-life. A study in six subjects showed approximately 70% of the administered radiolabeled DIPRIVAN Injection dose was recovered in the urine in the first 24 hours and approximately 90% of the dose was recovered in the urine within five days. DIPRIVAN is chiefly metabolized by conjugation in the liver to inactive metabolites which are excreted by the kidney. A glucuronide conjugation metabolite accounted for about 50% of the administered dose. The exact metabolic fate of DIPRIVAN and the sites of possible "extrahepatic" metabolism have not been identified.

and the sites of possible extranepatic metabolism have not been identified. The pharmacokinetics of DIPRIVAN injection do not appear to be altered by gender, chronic hepatic cirrhosis or chronic renal failure. The effects of acute hepatic or renal failure on the pharmacokinetics of DIPRIVAN have not been studied. With increasing age the clearance of DIPRIVAN decreases from a mean \pm S.D. of 1.8 \pm 0.4 l/m in in glority (65-60 years) patients. When given by an infusion for up to two hours, the pharmacokinetics of DIPRIVAN appear to be independent of dose (0.05-0.15 mg/kg/min) and similar to IV bolus pharmacokinetics. The steady state propofol blood concentrations are proportional to the rate of administration.

proportional to the rate of administration.

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics and narcotics) can increase the CNS depression induced by DIPRIVAN. Morphine premedication (0.15 mg/kg) with N₂0 67% has been shown to decrease the necessary DIPRIVAN Injection maintenance infusion rate and therapeutic blood concentrations, when compared to a nonnarcotic (lorazepam) premedication. An alfentamil infusion rate of 50 μg/kg/h has been shown to replace the anesthetic effects of N₂0 67% and morphine premedication. Intravenous injection of a therapeutic dose of DIPRIVAN Injection produces hypnosis rapidly and smoothly with minimal excitation, usually within 40 seconds from the stant of an injection (one arm-brain circulation time). As with other rapidly acting intravenous anesthetic agents, the half-time of blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia. Propolol blood concentrations required for mintenance of anesthesia have not been completely characterized. When ritrous goide, owen, and propolal are used for maintenance of general anesthesia, supplementation.

When nitrous oxide, oxygen, and propofol are used for maintenance of general anesthesia, supplementation with analgesic agents (eg. narcotics) is generally required; neuromuscular blocking agents may also be required. (See DOSAGE AND ADMINISTRATION.)

The hemodynamic effects of DIPRIVAN Injection during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease)

is maintained, the implicit calculation and in a preciable decrease in cardiac output. If ventilation is assisted or controlled (positive pressure ventilation), the degree and incidence of decrease in cardiac output are accentuated. Addition of a potent opioid (eg. fentanyl) when used as a premedicant further decreases cardiac output are accentuated. If anesthesia is continued by infusion of DIPRIVAN Injection, endotracheal intubation and surgical stimulation may return arterial pressure towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of DIPRIVAN during induction are generally more pronounced then with the properties of the

studies have shown that the removal and the studies of DPFN was obtained induction are generally more pronounced than with traditional IV induction agents. Insufficient data are available regarding the cardiovascular effects of DIPRIVAN Injection when used for induction and/or maintenance of anesthesa in elderly, hypovolemic, hypotensive, debilitated patients, patients with severe cardiac disease (ejection fraction < 50%) or other ASA III/IV patients. However, limited information suggests

cardiac disease (ejection fraction < 50%) or other ASA III/IV patients. However, limited information suggests that these patients may have more profound adverse cardiovascular responses. It is recommended that if DIPRIVAN Injection is used in these patients, a lower induction dose and a slower maintenance rate of administration of the drug be used. (See DOSAGE AND ADMINISTRATION.)

Clinical and preclinical studies suggest that DIPRIVAN Injection is rarely associated with elevation of plasma histamine levels and does not cause signs of histamine release. Induction of anesthesia with DIPRIVAN Injection is frequently associated with apnea. In 1573 patients who received DIPRIVAN Injection (2.0 to 2.5 mg/kg), apnea lasted 0-30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. During maintenance DIPRIVAN Injection (0.1 to 0.2 mg/kg/min) causes a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medications (eg, narcotics, sedatives, etc.).

Clinical studies in humans and studies in animals show that DIPRIVAN Injection does not suppress the adrenal

Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN Injection agesthesia produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic

Animal studies and limited experience in susceptible patients have not indicated any propensity of DIPRIVAN Injection to induce malignant hyperthermia.

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to the presented to the

reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known, (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have

DIPRIVAN® (propofel) Injection

not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN injection should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical

of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rate AS ill or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. Since DIPINUM Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the

recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two wellcontrolled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects, one accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Perioperative myoclonia, rarely including opistrotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg., atropine or gitycopyrroiate) to modify potential increases in vagal tone due to concomitant agents (eg., succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg., morphine, mependine, and fentaryl) and combinations of narcotics and sedatives (eg., benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg. isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection and pressures and cardiorespiratory effects of DIPRIVAN Injection and pre

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using Salmonella sp) mutation test, gene mutation/gene conversion using Saccharomyces cerevisiae, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fer-

tility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal feths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human

responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance.

DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxidension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled chinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incident million The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the ID/Casadia and the support and accurate estimate of their individual control in the control of the control of

included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1%—All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. Cardiovascular: Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. Central Nervous System: Movement.* Headache, Dizziness, Twitching, Bucking/Jerking/

Thrashing, Clonic/Myoclonic Movement. Digestive: Nausea.** Vomiting.* Abdominal Cramping. Injection Site: Burning/Stinging.** Pain.** Tingling/Numbness, Coldness. Respiratory: Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). Skin and Appendages: Flushing.

Incidence of unmarked events is 196-3%; "3% to 10%; "*10% or greater.

Incidence Less than 1% — Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are italicized.)

seen in clinical trials, are italicized.)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. Cardiovascular: Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. Central Nervous System: Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Fremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity, Digestive: Hypersalivation, Dry Mouth, Swallowing. Injection Site: Discomfort, Philebitis, Hives/Itching, Redness/Discoloration.

DIPRIVAN® (propofol) Injection

Musculoskeletal: Myalgia. Respiratory: Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. Skin and Appendages: Rash, Urticaria. Special Senses: Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. Urogenital: Urine

Incidence Less than 1% - Causal Relationship Unknown (Adverse events reported only in the literature, not

seen in clinical trials, are *Italicized.*)

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, Myocardial Ischemia. Central Nervous System: Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, Opisthotonus. Digestive: Diarrhea. Respiratory: Laryngospasm. Skin and Appendages: Diaphoresis, Pruritus, Conjunctival Hyperemia. Special Senses: Ear Pain, Nystagmus. Urogenital: Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressol

agents and/or anticholinergic agents.

The intravenous LD₅₀ values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated to the premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated to the premedicated of the premedicated of the property of the patients with the obligate signs should be to the premedicated of the patients with the obligate signs should be titrated. (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent

IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps

When administering DiPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DiPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DiPRIVAN injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%-50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. It vital sign changes and or provide and provide additional provides and controlled after a five minute period, other means such as a parcofic barbiturate vasodilator or inibalation or inpalation or inibalation or inib not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable

rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory

(le, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DiPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boliuses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION		
Induction	Dosage should be individualized. Adults: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patlents: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).		
Maintenance Infusion	Variable rate infusion — titrated to the desired clinical effect. Adults: Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).		
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.		

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because

united will 340 because injection, 654; and it should not be directed to a content ation less shall 2 high its an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

nnpation with the londwing intravenous hours when adminit - 5% Dextrose injection, USP - Lactated Ringers injection, USP - Lactated Ringers and 5% Dextrose injection - 5% Dextrose and 0.45% Sodium Chloride Injection, USP - 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection should be discarded at the end of the surgical procedure.

HOW SUPPLIED: DIPRIVAN Injection (NDC 0038-0290) is available in ready-to-use 20-mL ampules containing 10 mg/mL of propofol.

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from

light. Shake well before use Rev. Q 10/89

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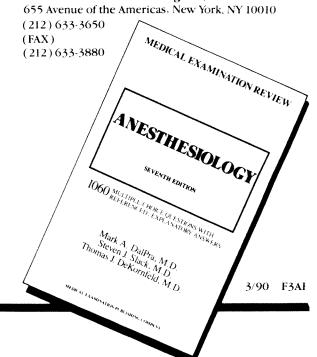
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erative pain relief using patient-controlled analgesia and continuous epidural infusions. Close collaborative relationships with MGH/Harvard colleagues in Medicine, Surgery, Psychiatry, Orthopedic Surgery, Neurology, Neurosurgery, Nursing, and Physical Therapy. Busy and expanding program. Salary commensurate with qualifications. (Staff level anesthesiologists may substantially increase compensation through other clinical activities.) Contact: Dr. Daniel Carr, Harvard University Department of Anesthesia at the Massachusetts General Hospital, Boston, MA 02114.

POSITION AVAILABLE IMMEDIATELY

For BC/BE anesthesiologist, southern New England, 50 minutes to Boston, seacoast, and ski areas. 200+-bed hospital. Salary first two years with partnership in professional corporation thereafter. Small size city with excellent schools. Group of MDAs and CRNAs. Excellent salary and benefits. Please send CV with references and salary expectations to Box 406.

406E/G

ANESTHESIOLOGIST

Department of Anesthesiology at the SUNY Health Science Center in Syracuse is recruiting faculty at the Instructor and Assistant and Associate Professor levels. Qualified individuals with a strong academic commitment in all types of anesthesia, critical care and pain management are sought. SUNY Health Science Center is a tertiary care center and provides clinical services also to the Syracuse Veterans Administration Hospital. Rank and salary are commensurate with experience. Must be board certified or board eligible and possess a New York State medical license. Please send letter, curriculum vitae, and names, addresses, and phone numbers of three references to Enrico M. Campore MD, Professor and Chairman, Department of Anesthesiology, SUNY Health Science Center, Syracuse NY 13210. The State University of New York Health Science Center at Syracuse is an Equal Opportunity/AA employer.

407E/G

UNIVERSITY OF LOUISVILLE

The Department of Anesthesiology has openings for all faculty ranks. Special consideration will be given for OB, critical care, and senior faculty with administrative duties (Vice-Chairman). The University of Louisville School of Medicine offers competitive salary and fringe benefits. Applicants please send curriculum vitae to B.M. Rigor, Sr, MD, Chairman of Department of Anesthesiology, School of Medicine, University of Louisville, Louisville, KY 40292.

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ANESTHESIOLOGIST

BC or BE. 250-bed hospital. All types of cases, modern equipment, 3 MDs/5 CRNAs, group practice. Recent graduates welcome. Family-oriented community. Medical Associates, PO Box 141, Minot, ND 58702.

NIH PAIN RESEARCH FELLOWSHIP

A two-year fellowship is available starting July 1991. Program will train board-eligible anesthesiologist for a career in academic research. Fellows will conduct studies of the neural mechanisms and neuropharmacology of pain and analgesia in patients with nerve injury, reflex sympathetic dystrophy, postoperative pain, cancer, and other conditions. Intensive training available in clinical trial design, quantitative sensory testing, use of computers, and experimental pain models. Fellowship includes consultation service for NIH Clinical Center and close interaction with large basic science group. Salary: \$37-41,000 each year. Send CV to Mitchell Max, MD, NIH/ NIDR Pain Research Clinic, National Institutes of Health, 9000 Rockville Pike, Building 10, Room 3C405, Bethesda, MD 20892; telephone: (301) 496-5483. NIH is an Equal Opportunity Employer.

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NEW YORK CITY

Opening for CA-4 Neuroanesthesia Fellow at the Neurological Institute, College of Physicians and Surgeons, Columbia University. Flexible starting date. Fellowship will include both clinical and research opportunities. Neuroanesthesiology group active in basic and clinical research including cerebral blood flow determination, autoradiography, pharmacokinetic/ pharmacodynamic modeling, and electrophysiological monitoring. The Neuroanesthesiology Service is responsible for the administration of approximately 1900 anesthetics per year including 800 intracranial procedures. Send CV to Edward D. Miller, Jr., MD, Professor and Chairman,

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Available beginning July 1990 in the Department of Anesthesiology at Hahnemann University. Year-long CA-3 positions may be customized to include obstetric anesthesia, cardiothoracic anesthesia, pain management, pediatrics, and advanced clinical training. Training for 6-12 months of cardiothoracic anesthesia in either the CA-3 or CA-4 year includes anesthetic management of adult and pediatric patients, training in intraoperative transesophageal echocardiography, and participation in on-going clinical research. Starting date negotiable. Send curriculum vitae to R.M. Padolina, MD, Residency Director, Department of Anesthesiology, Broad and Vine, Philadelphia, PA 19102.

414E

PAIN GROUP OPPORTUNITY

Unique opportunity for patient-oriented BC/BE anesthesiologist in free standing pain clinic. Will train. No OR or OB anes thesia responsibility, relaxed clinic setting with emphasis on comprehensive evaluation and the use of neural blockade. Excellent salary and benefits, good hours and vacation time. Contact David P. Ellis, MD, 4101 Classen Boulevard, Suite E, Oklahoma City, OK 73118; (405) 524-0044.

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Anesthesiologist BC/BE needed immediately for incorporated group of six MD anesthesiologists in 581-bed medical center. All types of anesthesia except OH. Excellent financial package first year leading to partnership. Send CV to Anesthesiology Associates of SE Michigan MD, PC, 1011 Patrick Street #19, Flint, MI 48503.

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Opening for board-certified anesthesiologist to join four MDs and six CRNAs in 190-bed modern community hospital. All types of surgery except cardiac. Moderate obstetrics. Must be energetic and good with epidurals and invasive lines. Excellent fringe benefits and early partnership. One hour drive to seacoast, ski resorts, and Boston. Send CV to Prospect Anesthesia Services, P.C., 10 Prospect Street, Nashua, NH 03060.

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ANESTHESIOLOGIST

Board certified, one-year fellowship in OB anesthesia, ASAP. Call (301) 365-7580 or write Director of Anesthesia, Columbia Hospital for Women, 2424 L Street NW, Washington, DC 20037.

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ANESTHESIA

A vacancy exists for a Canadian licenced anesthetist with FRCPC or eligibility for same, to join the academic staff of Memorial University of Newfoundland, Faculty of Medicine. Clinical responsibilities would be primarily at the General Hospital-Health Sciences Centre, which is the adult tertiary care center for the province of Newfoundland and Labrador. The hospital has a well-developed multidisciplinary intensive care unit and a pain clinic in which the Discipline of Anesthesia has a high profile. The Discipline of Anesthesia has a major interest in the university's newly established hyperbaric facility, which consists of a four-chamber diving complex (including a vertical wet chamber) rated at 1000 feet of seawater depth and capable of mixed gas saturation diving as well as hyperbaric oxygen therapy. An interest in research is essential; a special interest in hyperbaric medicine would be an advantage. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents of Canada. Write for further information to Henry J. Manson, MB, ChB, FFARCS, FRCPC, Professor and Chairman, Discipline of Anesthesia, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, Canada AIB 3V6.

421E

FLORIDA

Anesthesiologist wanted for part time. Salary negotiable plus benefits. Phone (904) 252-7879.

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NEBRASKA

Practice Opportunity: Board-eligible anesthesiologist for a well-established two-MD, four-CRNA practice in rural Nebraska. Full benefits upon employment. Partnership opportunity. No neuro- or cardiac surgery. Good hunting, fishing, and family conditions in central Nebraska. Write: Hastings Anesthesiology, 608 West 6th, Hastings, NE 68901.

423E

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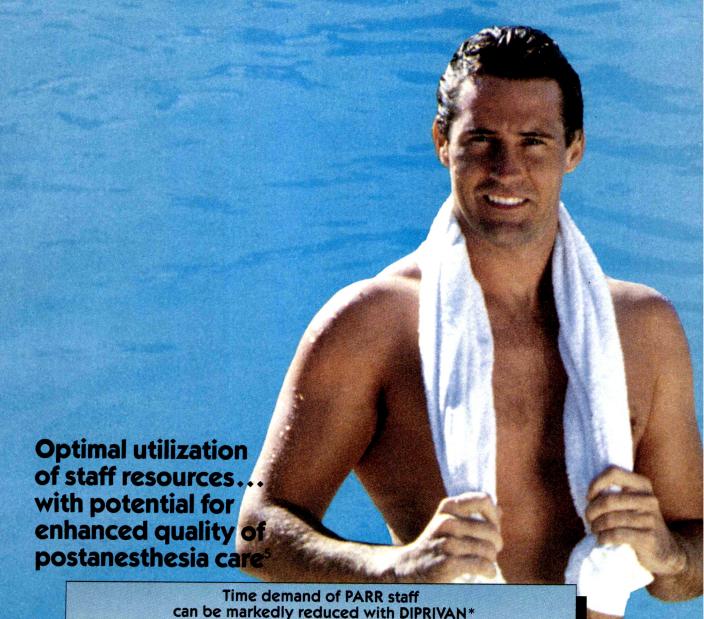
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OR SALE

North American Drager Narkomed 3 anesthesia machine. Excellent condition, fully loaded. Call for specifications. Reasonably priced. (901) 682-0822.

415E



Time demand of PARR staff can be markedly reduced with DIPRIVAN*					
Mean time of direct patient care required of all recovery	DIPRIVAN	Thiopental/isoflurane	Difference		
room staff (per patient)	45.8 min	64.6 min	-18.8 min		
Total direct patient-care time required of <i>all</i> recovery room staff (per day)	00 £ L				
room starr (per day)	20.6 h	29.1 h	-8.5 h		

^{*}Conclusions drawn from an economic model applied to clinical data. Economic model assumptions: operating rooms—5; patients per day—27; anesthetic regimen—100% DIPRIVAN versus 100% thiopental/isoflurane; staffing level—1 nurse for 1 patient in Phase I, 1 nurse for 3 patients in Phase II.⁵

Additional benefits beyond the recovery room for inpatients

DIPRIVAN may allow more efficient use of valuable nursing service time during extended postop stays, when patients may be able to:

ambulate earlier¹

- ingest fluids earlier¹ and eat sooner 6
- return to routine self-care activities more rapidly



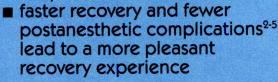
DIPRIVAN® INJECTION proposol 10 mg/mL

The benefits of DIPRIVAN may extend beyond the hospital

Once home, patients may resume day-to-day activities sooner—

a recovery profile with less of the nausea and vomiting associated with standard anesthetic agents²⁻⁵

■ a rapid return to normal diet⁶



DIPRIVAN: the costeffective alternative to standard induction agents and volatile maintenance agents

REFERENCES: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. 2. Cork RC, Scipione P, Vonesh MJ, Magarelli JL, Pittman RG. Propofol infusion vs. thiopental/isoflurane for outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A563. Abstract. 3. Weinigarten M, Youngherg JA. a multicenter, comparative study of Diprivan for the induction and maintenance of anesthesia by repeat bolius administration versus thiopental sodium for induction followed by inhalation anesthesia for maintenance. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 4. Youngberg JA, Ramadhyani U, Texidor M, Price J, Kay L, Findley E. Recovery following propofol vs isoffurane anesthesia in procedures longer than ninety minutes. Abstract. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 5. Marais ML, Maher MW, Wetchler BV, Korttila K, Apfelbaum JL. Reduced demands on recovery room resources with propofol (Diprivan) compared to thiopental-isoflurane. *Anesthesiol Rev.* 1989; 16(1):29-40. 6. Kay B. Recovery from Diprivan (propofol): European experience. *Semin Anesth.* 1988;7 (suppl 1):127-130.



EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because

compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradypardia. Treatment may include increasing the rate of international forms and the property files. the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or adminis-tration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the

awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous secuelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the fore-

arm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcuta-neous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in

which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included

anticholinergic agents (eg. atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg. succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or

or intravenous premedication, particularly with narcotics (e.g., morphine, reperdidine, and fertanny) and combinations of narcotics and sedatives (e.g., benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according the decirity of the order of the properties of the properties

to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg. ni-trous oxide or opioids). The concurrent administration of potent inhalational agents (eg. isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of

the commonly used neuromuscular blocking agents (eg. succirylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed

with propotol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propotol. Tests for mutagenicity included the Ames (using Saimonella sp) mutation test, gene mutation/gene conversion using Saccharomyces cerevisae, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired tertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category 8: Reproduction studies have been performed in rats and rabbits at intravenous doses. The mg/kg/day for 5 days and have revealed no evidence of impaired.

15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the ofspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN injection is not recommended for obstetrics, including cesarean section deliveries,

because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are

diatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established

effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are presented by a correction processor.

when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical

study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 15/73 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient

DIPRIVAN® (propotol) Injection

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DIPRIVAN.

4

EMULBION FOR

5x20 mL Ampules

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

within each body system in Order of decreasing frequency.

Incidence Greater than 1%—All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. Cardiovascular: Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia,
Hypotension. Central Nervous System: Movement, "Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. Digestive: Nausea: "Vomiting," Abdominal Cramping, Injection Site:

Burning/Stinging.** Pain.** Tingling/Numbness, Coldness, Respiratory: Cough, Hiccough, Apnea (see also Burning/Stinging.** Pain.** Tingling/Numbness, Coldness. Respiratory: Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). Skin and Appendages: Flushing. Incidence of unmarked events is 196-396. "39% to 196." *109% or greater. Incidence Less than 194 — Causal Relationship Probable (Adverse events reported only in the literature, not

seen in clinical trials, are italicized.)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. Cardiovascular: Tachycardia, Permature Ventricular Contractions, Premature Arial Contractions, Syncope, Ahonormal ECG, ST Segment Depression. Central Nervous System: Shivering, Somnclence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity, Digestitor, Hypersalivation, Dry Mouth, Swallowing, Injection Site: Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. Musculoskeletal: Myalgia. Respiratory: Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat. Sneezing, Tachypnea, Hyperventilation, Hypoxia. Skin and Appendages: Rash, Urticaria. Special Senses: Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. Urogential: Urine Retention, Green Urine.

Incidence Less than 1% - Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are italicized.)

seen in clinical trials, are *Italicized*.)

Cardiovascular, Arrhythmia, Bigerniny, Edema, Ventricular Fibrillation, Heart Block, Myocardial Ischemia. Central
Nervous System: Anxiety. Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures,
Opisthotonus. Digestive: Diarrhea. Respiratory: Laryngospasm. Skin and Appendages: Diaphoresis, Pruntus,
Conjunctival Hyperemia. Special Senses: Ear Pain, Hystagrmus. Urogenital: Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs,
DIPRIVAN Injection administration should be discontinued immediately. Overdosage is

likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning

by artificial vertiliation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patients legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents.

The intravenous LD₅₀ values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patients age and clinical status. Most adult patients under 55 years of age and classified ASAI and II are itsely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzoldazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be

titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent

IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps

or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%-50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie. intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory

anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to avoid administration of DIPRIVAN Injection at rates.

maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, and producing an elegativities of the producing of the

scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION			
Induction	Dosage should be individualized. Adults: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).			
Maintenance Infusion	Variable rate infusion — titrated to the desired clinical effect. Adults: Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).			
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.			

HOW SUPPLIED: DIPRIVAN Injection (NDC 0038-0290) is available in ready-to-use 20-mL ampules containing

10 mg/mL of propofol.

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use

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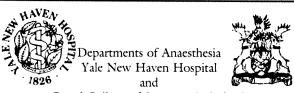
The person must be committed to excellence in clinical care, teaching and basic science or clinical research. An individual who has completed ABA Certification and a Pain Fellowship is preferred. Academic rank and salary will be commensurate with qualifications.

New York State License is necessary.

Send Curriculum Vitae to:

RONALD A. GABEL, M.D.
Professor and Chairman
or
RICHARD B. PATT, M.D.
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Epinephrine and Phenylephrine Increase Cardiorespiratory Toxicity of Intravenously Administered Bupivacaine in Rats

Jay R. Kambam, мр, Wesley W. Kinney, мр, Fumiko Matsuda, мр, William Wright, вѕ, and Duncan A. Holaday, мр

KAMBAM JR, KINNEY WW, MATSUDA F, WRIGHT W, HOLADAY DA. Epinephrine and phenylephrine increase cardiorespiratory toxicity of intravenously administered bupivacaine in rats. Anesth Analg 1990;70:543–5.

We studied the effects of epinephrine and phenylephrine on the cardiorespiratory toxicity of intravenously injected bupivacaine in Sprague-Dawley rats. Our data show that both epinephrine and phenylephrine significantly increased cardiorespiratory toxicity of intravenously injected bupivacaine (P < 0.007, χ^2 analyses with Yates' correction). Our data suggest that epinephrine or phenylephrine added to bupivacaine may be more toxic to cardiorespiratory systems than plain bupivacaine or epinephrine alone or phenylephrine alone when injected intravenously in rats.

Key Words: ANESTHETICS, LOCAL—bupivacaine. TOXICITY, BUPIVACAINE. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—epinephrine, phenylephrine.

Bupivacaine, an amide-type local anesthetic, is frequently used for various types of regional anesthesia. Epinephrine (frequently) or phenylephrine (infrequently) is added to a local anesthetic solution to prevent rapid vascular absorption and/or to prolong the duration of local anesthetic action (1). Epinephrine is also believed to antagonize the cardiovascular depressive effects induced by local anesthetics (2). The purpose of the present study was to investigate whether the addition of epinephrine or phenylephrine to bupivacaine protects from cardiorespiratory toxicity induced by intravenously administered bupivacaine.

Methods

Fifty adult male Sprague–Dawley rats weighing approximately 300 g were randomly divided into five groups of 10 each. Rats were anesthetized with 40–60

mg/kg of intraperitoneal pentobarbital, a femoral vein was cannulated, and baseline femoral blood gas tensions were measured. Our preliminary doseresponse experiments in rats showed that a 4-4.5-mg/ kg dose of 0.5% plain bupivacaine when injected intravenously is fatal in at least 25% of the rats. Based on our preliminary experiments bupivacaine (0.5% solution, 4 mg/kg IV) was chosen and given as either plain solution (group 1), with 1:200,000 epinephrine (group 2), or with 1:200,000 phenylephrine (group 3) over 5 s to see whether epinephrine or phenylephrine protects from bupivacaine-induced cardiorespiratory toxicity. In groups 4 and 5 normal saline was substituted for bupivacaine and was given with 1:200,000 phenylephrine (group 4) and 1:200,000 epinephrine (group 5). Experiments were performed between 9 AM and 12 noon to avoid diurnal variations. Respirations and heart rate and rhythm (ECG lead II) were monitored throughout the experiment using a Hewlett Packard ECG monitor. Precordial pulsations were also observed with an illuminated magnifying lens. Rats were not ventilated or oxygenated to mimic the usual clinical situation of bupivacaine-induced cardiorespiratory toxicity. Rats were classified as survivors or fatalities at 1 min after the administration of intravenous bupivacaine. Rats that sustained adequate ventilation, color, and heart rate were classified as survivors, and rats that developed apnea, cyanosis, and agonal rhythm with no cardiac impulse were

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Table 1. Group Characteristics at Baseline

1990:70:543-5

	Group 1	Group 2	Group 3	Group 4	Group 5
Weight (g)	294 ± 8	290 ± 6	282 ± 6	284 ± 6	283 ± 5
Barb (mg/kg)	51 ± 6	64 ± 8	61 ± 7	58 ± 5	60 ± 9
pΗ	$7.45 \pm .01$	$7.45 \pm .01$	$7.46 \pm .05$	$7.44 \pm .01$	$7.45 \pm .01$
Pco ₂ (mm Hg)	46 ± 1	42 ± 2	45 ± 1	45 ± 1	47 ± 2
Po ₂ (mm Hg)	46 ± 2	47 ± 2	44 ± 1	47 ± 2	44 ± 1
BE (mEq/L)	7 ± 1	6 ± 2	9 ± 1	8 ± 1	6 ± 2

Barb, pentobarbital; BE, base excess.

The mean (\pm sem) baseline blood gas tensions, weights, and pentobarbital doses are shown for the rats that received plain bupivacaine (group 1, n = 10), bupivacaine with epinephrine (group 2, n = 10), bupivacaine with phenylephrine (group 3, n = 10), saline with phenylephrine (group 4, n = 10), and saline with epinephrine (group 5, n = 10).

P = not significant, ANOVA.

classified as dead. The survivors were killed with an additional toxic dose of bupivacaine.

Data on body weights, pentobarbital doses, and baseline blood gas tensions were analyzed using analysis of variance (ANOVA). Survival rates were analyzed using χ^2 analyses with Yates' correction. A *P*-value of <0.05 was considered statistically significant.

Results

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Two of 10 (20%) rats in group 1, 9 of 10 (90%) in group 2, 9 of 10 (90%) in group 3, none of 10 in group 4, and none of 10 in group 5 died of cardiorespiratory arrest $(P < 0.007, \chi^2 \text{ analysis with Yates' correction})$. There were no significant differences in the baseline blood gas tensions, weights, or pentobarbital doses between the five groups (ANOVA) (Table 1). All rats in groups 1, 2, and 3 became apneic and developed tachyarrhythmias within about 10 s after intravenous bupivacaine injection. The rats that survived spontaneously converted back to regular sinus rhythm and resumed spontaneous ventilation within about 10 s and maintained regular heart rate and good color. The rats that did not survive remained apneic, became cyanotic, and developed bizarre ventricular arrhythmias leading to agonal rhythm and cardiac arrest within 40-45 s after intravenous bupivacaine injection. Almost all rats given bupivacaine with either epinephrine or phenylephrine initially developed marked ventricular arrhythmias including ventricular tachycardia and/or ventricular fibrillation, followed by agonal rhythm leading to asystole. Rats given plain bupivacaine typically developed apnea and supraventricular tachycardia with atrioventricular conduction abnormalities for 10-12 s followed by sinus rhythm and resumption of spontaneous ventilation. All rats given epinephrine in saline and phenylephrine in saline survived, and none of these rats developed any cardiac arrhythmias. None of the rats in the phenylephrine-alone group (group 4) developed apnea. Only one rat in the epinephrine-alone group (group 5) developed apnea, which lasted about 10 s. Even though we classified rats as either survivors or fatalities at the end of 1 min the results were the same even after several minutes.

Discussion

Our results show that either epinephrine or phenylephrine containing bupivacaine has greater cardiorespiratory toxicity than plain bupivacaine or epinephrine or phenylephrine in saline when administered intravenously. Our present results apply only to inadvertent intravenous administration of bupivacaine. Our data in no way suggest that bupivacaine has a greater cardiorespiratory toxicity when epinephrine or phenylephrine is added to it and injected by infiltration, subcutaneously, intramuscularly, or about nerve roots, or when injected into the epidural space. It is common practice to add epinephrine to the local anesthetic used for regional anesthesia. The reasons for adding epinephrine to local anesthetics are threefold (3,4). First, epinephrine prolongs the duration of action of local anesthetic. Second, epinephrine decreases the blood concentration of local anesthetic by delaying the absorption of local anesthetic into the blood. Third, epinephrine improves the quality of the nerve block. It is also common belief among some anesthesiologists that epinephrine protects from cardiac depression induced by local anes-

Bupivacaine, when injected accidentally into the vascular system, probably has the greatest cardiorespiratory toxicity of local anesthetic agents in use today (5,6). Bupivacaine is, nevertheless, widely used for epidural anesthesia in both pregnant and nonpregnant patients because of its unique properties of long duration of action and excellent analgesia (7). The fact that the ratio between bupivacaine concen-

trations in umbilical vessels and maternal venous blood is low (0.2–0.4), the half-life in the neonate is short, and there are no neurobehavioral changes in neonates of mothers who received epidural bupivacaine makes bupivacaine safer for the fetus than other local anesthetics (7).

The exact mechanism for the bupivacaine-induced cardiorespiratory toxicity is not known. Previous investigators suggest that it may involve both fast (sodium-dependent) and slow (calcium-dependent) channels in the heart (8,9). Epinephrine is known to cause cardiac dysrhythmias when injected in the presence of certain general inhalation anesthetics (10,11). We have not investigated the mechanism for the potentiation of bupivacaine-induced cardiorespiratory toxicity by epinephrine or phenylephrine. Bupivacaine, at high blood concentrations, is known to increase systemic and pulmonary vascular resistance and possibly causes coronary vasoconstriction (12-14). We speculate that epinephrine and phenylephrine further increase the vascular resistance and contribute to bupivacaine-induced cardiorespiratory toxicity. Epinephrine by phosphorylation of the calcium channel via cyclic adenosine monophosphatedependent kinase increases the probability of finding the calcium channel in the open form in the cardiac muscle and may contribute to the potentiating action of bupivacaine by making more calcium channels available to bupivacaine (15).

Bernards et al. reported in a recent paper that the addition of epinephrine to bupivacaine did not alter the dose of bupivacaine that causes cardiovascular collapse in awake spontaneously breathing pigs but did decrease the dose of bupivacaine that causes seizures and dysrhythmias (16). Their results clearly show that epinephrine did not protect the animals from bupivacaine-induced cardiovascular collapse. Marked variations in the methodology might have accounted for some of the differences in our results. For example, Bernards et al. injected bupivacaine with a pressure infusion pump at a rate of 2 $mg \cdot kg^{-1} \cdot min^{-1}$ for a period of more than 3 min. We administered bupivacaine as a single bolus injection in less than 15 s. We noted apnea as the first sign of systemic toxicity from intravenously administered bupivacaine in our rat model. Bernards et al. did not report the respiratory status of their animals with continuous administration of intravenous bupivacaine. Their animals were acidotic (pH around 7.24) compared to our animals (pH around 7.45) before the cardiovascular collapse.

Our results show that both epinephrine and phenylephrine increase intravenously injected bupivacaine-induced cardiorespiratory toxicity in rats.

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Review Article

Perioperative Management of the Multiorgan Donor

Kerri M. Robertson, MD, FRCP(C), and D. Ryan Cook, MD

Key Words: SURGERY, TRANSPLANTATION.

With recent advancements in tissue procurement and preservation, surgical techniques, and immunosuppression, transplantation of vital human organs has become a life-saving therapy for patients suffering from end-stage organ failure. There is a calculated annual need for 40-50 kidney transplants per million people (1,2). The estimates for heart and pancreatic transplants run about one-third of this figure (3), and the total number of potential liver recipients in the United States may approximate 25,000 patients per year (4). The community donor pool consists of any medical unit with surgical facilities accessible by air or ambulance within a time interval from the recipient institution dictated by the allowable cold ischemia time of the donor organ. As such, every anesthesiologist should be prepared to provide optimum perioperative care for postmortem donor surgery.

It is the purpose of this article to discuss the medical, surgical, and anesthetic care of the multiorgan donor. By highlighting problems peculiar to the brain-dead donor and the basics of organ procurement and preservation, the physician will gain an understanding of factors leading to end-organ damage and therapeutic methods of protection from such injury. Early graft dysfunction whether from ischemic injury, primary nonfunction, or rejection may necessitate immediate retransplantation or result in early death of the recipient.

Living related renal or bone-marrow donors and brain-dead patients are currently our only donor

Diagnosis of Brain Death

Understanding the concept of brain death without cardiac death is crucial for successful recovery of organs for transplantation. In brain death, the irreversible cessation of total brain function is the primary event as defined by profound coma, unresponsiveness to noxious stimuli, and the absence of brainstem function (7). Cardiorespiratory and other essential organ functions are temporarily sustained with mechanical support and resuscitative measures.

sources. While under the care of an anesthesiologist, vital organs including the liver, small bowel, heart,

heart-lungs, kidneys, or pancreas are retrieved. In general, donors are previously healthy individuals

who have suffered an irreversible catastrophic brain injury of known etiology, with no history of disease

or trauma involving the organs considered for dona-

tion. Ideally, there should be cardiovascular stability

requiring minimum inotropic support with no epi-

sodes of prolonged hypotension, ischemia, hypother-

mia, hypovolemia, or cardiac arrest in excess of 15

min. Attempts to correlate donor factors with trans-

plantation outcome have been unsuccessful, and re-

covery from such episodes may therefore indicate

satisfactory organ function without permanent injury

and necessitate reassessment of the donor's suitabil-

ity (5,6).

The clinical diagnosis of brain death is made when all of the following criteria have been satisfied (8,9):

1. Coma of established and irreversible etiology in the absence of potentially reversible causes including drug intoxication (barbiturates, sedatives, hypnotics, and alcohol), treatable metabolic disorders, hypothermia (core temperature <32.2°C), shock, and peripheral nerve or muscle dysfunction due to disease or neuromuscular blocking drugs.

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- No spontaneous muscular movement. Patients
 often retain or regain spinal reflexes, which are
 intact neural arcs functioning independent of central regulation. Therefore, spinal level movements
 such as deep tendon or plantar reflexes may be
 elicited.
- 3. Absent cranial nerve reflexes and responses. The pupils must be nonreactive to light stimuli with absent corneal, vestibuloocular, occulocephalic, pharyngeal, and respiratory reflexes. No motor response to painful stimuli within the cranial nerve distribution should be present. The pupils should be midsize or larger. Care must be taken to assure that atropine or related drugs that could block the pupillary response to light have not been given to the patient.
- 4. Atropine resistance as indicated by a failure to increase the heart rate by more than 5 beats/min after the administration of atropine sulfate intravenously in a dose of 0.04 mg/kg. The drug should be administered by a central route free of other chronotropic drugs, thus preventing spurious results on testing. Theoretically, loss of the vagal motor nucleus would then abolish tonic vagal activity and annul the anticholinergic effect of atropine on the heart (10).
- 5. A positive apnea test. Apnea was originally defined as an absence of spontaneous breathing movements for 3 min when the patient was disconnected from ventilatory support. This may not allow sufficient time for hypercarbic stimulation of central respiratory control centers, as the Paco₂ threshold for respiratory stimulation in a comatose patient may be elevated to as high as 50-60 mm Hg, and many ventilatory support-dependent patients have low Paco₂ levels that rise slowly during interruption of ventilation (11). The etiology of an observed decrease in oxygen consumption and carbon dioxide production includes absence of brain metabolism and central sympathetic stimulation, decreased muscle tone, hypothermia, and the absence of several major sources of oxygen utilization. Hypercarbia adequately stimulates respiratory effort within 30 s, when the Paco₂ exceeds 60 mm Hg. A safe way of testing the function of the medullary respiratory center involves a trial of apneic (diffusion) oxygenation, where after the interruption of ventilatory support in the presence of a $Paco_2 > 55-60$ mm Hg there is no evidence of spontaneous respiratory movements. In addition, a history suggestive of dependence on a hypoxic stimulus for ventilation requires that the Pao2 at the end of the test must be <50 mm Hg.

If blood gas determinations are available, the Paco₂ should be 40 ± 5 mm Hg and the pH should be 7.35–7.45 before testing for apnea begins. The patient should be preoxygenated with 100% oxygen for 10 min before testing. While continuously monitoring the arterial blood pressure, heart rate and rhythm, and, ideally, the end-tidal concentration of carbon dioxide and capillary oxygen saturation, the respirator is discontinued for 10 min. To prevent hypoxemia, 100% oxygen is insufflated at 12 L/min through a catheter positioned in the endotracheal tube, proximal to the carina. Observation is made for small volume respirations. Blood gas measurements are made at baseline and at 5 and 10 min, followed by resumption of mechanical ventilation. If blood gas determinations are not available, an adequate test of brainstem responsiveness to hypercarbia can be provided by ventilating the patient for 10 min with a 95% oxygen, 5% CO₂ mixture before the 10-min apneic oxygenation.

Testing for apnea without passive oxygenation is not recommended. In addition to its potentially deleterious effect on the brain, which may worsen a precarious but reversible neurologic insult, resultant hypoxemia can occasionally cause complex movements of the limbs and trunk, presumably due to spinal cord ischemia, that could be confused with reflex movements of cerebral origin.

Confirmatory tests to provide supportive evidence in the clinical determination of brain death include an isoelectric electroencephalogram and the demonstration of an absence of cerebral blood flow.

Preoperative Management of the Donor

The most important goals of preoperative management of the potential donor are hemodynamic stabilization and support of body homeostasis in the intensive care unit (12–15). There are few prospective studies to substantiate a great deal of the dogma followed in the care of the brain-dead donor, which leaves us with a tremendous amount of flexibility in how best to achieve very simple therapeutic goals. Basic points of management include continuing care of the patient's primary condition, with a shift in emphasis from cerebral resuscitation and intravascular volume contraction to maintenance of adequate cellular oxygenation and perfusion, while anticipating the normal physiologic sequelae of brain death (16). It may be useful to think of the organs as already belonging to the recipient and to accord them all the therapeutic intervention, no matter how costly, that would be afforded the recipient. Common problems in the care of the organ donor include hypotension,

Table 1. Normal Sequelae of Brain Death

Sequela	Cause	Management
Hypotension	Neurogenic shock; hypovolemia	Maintain intravascular volume; inotropic support—in order of preference: dopamine $\leq 10~\mu g \cdot k g^{-1} \cdot min^{-1}$ dobutamine $\leq 15~\mu g \cdot k g^{-1} \cdot min^{-1}$ epinephrine $\leq 0.1~\mu g \cdot k g^{-1} \cdot min^{-1}$ norepinephrine and dopamine 2–4 $\mu g \cdot k g^{-1} \cdot min^{-1}$.
Arrhythmia-bradycardia	CNS injury; hypothermia; abnormal electrolytes or blood gases; myocardial ischemia	Atropine resistant; use chronotropic drugs or temporary venous pacing
Hypoxemia	Central or pulmonary	$Pao_2 = 100-150 \text{ mm Hg}$ $Paco_2 = 35-45 \text{ mm Hg}$ pH = 7.35-7.45 $PEEP \le 7.5 \text{ cm H}_2O$ $F1_{o_2} \le 0.40 \text{ (heart-lungs)}$
Diabetes insipidus	Pituitary or hypothalamic dysfunction	Volume replacement; vasopressin (0.1 U/min infusion) or DDAVP (0.3 µg/kg IV) to maintain a urine output of 1.5–3 mL·kg ⁻¹ ·h ⁻¹ ; correct electrolyte disorders; inotropic support
Hypothermia	Loss of hypothalamic temperature regulation	Early aggressive warming to maintain the temperature above 34°C
Anemia	Hemorrhage; hemodilution	Transfuse to keep the hematocrit >30%

DDAVP, desmopressin acetate; CNS, central nervous system.

arrhythmias, respiratory-related disorders, diabetes insipidus (DI), sepsis, hypothermia, anemia, and endocrine abnormalities (Table 1).

Hypotension

Brainstem death results in the breakdown of effective central regulatory mechanisms. In patients being mechanically supported, despite optimum therapeutic intervention, cardiac death usually occurs within 48-72 h of brain death (17). Hypotension and hemodynamic instability secondary to neurogenic shock and hypovolemia should be anticipated in all donors (18). Neurogenic shock is caused by defective vasomotor control with subsequent progressive loss of systemic vascular resistance and pooling of the intravascular volume in the venous capacitance vessels (16). Causes of hypovolemia include therapeutic dehydration for cerebral edema, hemorrhage, DI with massive diuresis, inadequate replacement of essential and third-space fluid losses, and osmotic diuresis due to hyperglycemia, mannitol, or systemic radiocontrast dyes. Left ventricular dysfunction, brainstem herniation, hypothermia, and endocrine abnormalities may also be contributory.

Aggressive therapy directed at restoring and maintaining intravascular volume consists of vigorous hydration with colloid or crystalloid solutions and the

use of vasoactive drugs if needed, on a temporary basis. Goals for hemodynamic stabilization include volume expansion with normal saline or lactated Ringer's solution in 5-mL/kg boluses every 5-10 min until the systolic blood pressure exceeds 100 mm Hg (mean arterial pressure >70 mm Hg) or a central venous pressure of 12 cm H₂O is reached, with a normal sinus rhythm of <100 beats/min. It is important to avoid overhydration, for overhydration may then precipitate pulmonary edema, cardiac overdistention, and liver congestion with cellular injury during hypothermic preservation. More rapid volume expansion can be achieved using colloid or salt-poor albumin. The ideal choice of solution is a matter of dispute. Several centers are promoting the use of dextran 40 in combination with lactated Ringer's or normal saline with proposed benefits including maintenance of blood and plasma volume, moderate hemodilution, improved microcirculation and tissue oxygenation, and a decreased risk of thromboembolic complications (19,20). Use of vasopressor agents may be required initially for cardiovascular support, but ideally should be discontinued before organ retrieval to avoid peripheral vasoconstriction and disruption of regional blood flow with possible ischemic end-organ injury. In order of preference, the choice of agents for inotropic support of the myocardium are dopamine at $<10 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, dobutamine at <15 μ g·kg⁻¹·min⁻¹, epinephrine at <0.1 μ g·kg⁻¹·min⁻¹ and, in dire straits, an infusion of norepinephrine with dopamine at 2–4 μ g·kg⁻¹·min⁻¹ for protective renal vasodilation. Isoproterenol, with resultant tachycardia, may be especially useful in pediatric donors because of their fixed stroke volume and rate-dependent cardiac output. Use of predominantly α -adrenergic vasopressors such as metaraminol, phenylephrine, or norepinephrine should be avoided as they may cause severe peripheral vasoconstriction (21).

Dopamine dilates renal and mesenteric blood vessels at low doses $(1-2 \mu g \cdot kg^{-1} \cdot min^{-1})$ that may not increase the heart rate or blood pressure. Generally, doses from 2 to 10 μ g·kg⁻¹·min⁻¹ have predominantly β -adrenergic receptor stimulating properties that result in an increase in cardiac output, with the increase in systolic pressure greater than that of diastolic pressure, and a slight increase in heart rate without marked peripheral vasoconstriction or an increase in pulmonary artery pressure. At doses >10 $\mu g \cdot kg^{-1} \cdot min^{-1} \alpha$ -agonist activity is predominant (22). Administration of dopamine to infants may require significantly larger doses than those needed in adult donors to maintain an adequate perfusion pressure, presumably owing to catecholamine receptor immaturity or deficiency (23). At these higher doses (i.e., 15 vs 5 μ g·kg⁻¹·min⁻¹ in an adult) there seems to be no adverse effects on the glomerular filtration rate or urinary output (24).

The use of dopamine is not preferred by some institutions where the heart is considered for transplantation on the basis of two theoretical concerns: an iatrogenic catecholamine-induced donor cardiomyopathy (25) and catecholamine depletion of the myocardium through endogenous release of norepinephrine (26). There is experimental evidence that during the insidious development of brain death, hemodynamic changes, myocardial injury, and pulmonary edema may be induced by sympathetic activity. During the agonal period endogenous catecholamine release within the myocardium and peripheral vessels is induced by a period of accelerated sympathetic activity. This may culminate in structural damage to the heart from sequestration of calcium in the sarcoplasmic reticulum and a decrease in coronary perfusion pressure secondary to tachycardia (27). Such myocardial and pulmonary damage may contribute to primary nonfunction of the transplanted heart or lungs, which has been reported to occur with an incidence of <5%. The use of inotropic agents may augment this process, and they are best avoided or titrated to effect using minimum doses.

Dobutamine has primarily β -adrenergic receptor

stimulating effects that increase myocardial contractility and heart rate and frequently induce reflex peripheral vasodilation. There are no known direct effects on renal, splanchnic, or liver blood flows, although an increase in cardiac output may produce a secondary increase in renal blood flow. At doses >15 $\mu g \cdot k g^{-1} \cdot min^{-1}$, several undesirable effects can occur. Tachycardia, dysrhythmias, excessive increases in blood pressure, and a decrease in systemic vascular resistance with mild venodilation are possible (28).

The use of isoproterenol as an inotrope is limited by tachycardia, which may induce or exacerbate myocardial ischemia and cause renal vasoconstriction, hypotension, and possibly an insufficient coronary perfusion pressure secondary to a decrease in the diastolic blood pressure (29).

Epinephrine has mixed α - and β -stimulating properties, with predominantly β at low infusion rates. Its vasoactive effects are dose-dependent, and, at high concentrations, it causes a marked decrease in renal blood flow and glomerular filtration rate with a reduction in liver blood flow and blood volume (30). Recently, prolonged maintenance of hemodynamic stability with resultant normal liver and renal laboratory functions has been reported with the combined administration of vasopressin and low-dose epinephrine (31).

In the unlikely event of donor surgery involving only cardiac retrieval, the best choice of an inotrope would be an α -adrenergic agent to maintain the coronary perfusion pressure and limit the increase in myocardial oxygen consumption and the change in coronary artery flow induced by changes in heart rate.

Arrhythmias and Electrocardiographic Abnormalities

ST- and T-wave changes may be seen in patients with intracranial injury. These findings are of no pathologic significance but may be confused with electrocardiographic changes suggestive of myocardial ischemia. Atrial or ventricular arrhythmias and various degrees of conduction block occur with varying frequency in the organ donor (32). These arrhythmias may result from electrolyte and arterial blood gas disorders, loss of the vagal motor nucleus, increased intracranial pressure, drug therapy, myocardial ischemia, hypothermia, or ventricular irritability from cardiac contusion. Appropriate therapeutic intervention should be implemented. Bradycardia is not a problem unless it contributes to hypotension, and may be treated with dopamine, dobutamine, isopro-

terenol, or temporary venous pacing. Despite aggressive therapeutic efforts, all brain-dead patients will eventually undergo terminal arrhythmias that are resistant to therapy. The incidence of bradycardic episodes and asystole as the terminal cardiac rhythm is greater in children than in the adult population, where ventricular fibrillation is more common. This may be due to an immature autonomic nervous system and smaller muscle mass in the younger age group (33).

Respiratory-Related Problems

Pneumonia, pulmonary edema, aspiration, atelectasis, pneumothorax or hemothorax, or residual effects of the morbid event may decrease pulmonary compliance and impede alveolar gas exchange resulting in hypoxemia. The Fig. and minute ventilation should be such as to assure that the Pao₂ is 100–150 mm Hg, the arterial saturation is >95%, Paco₂ is 35–45 mm Hg, and pH is 7.35–7.45. PEEP levels in excess of 7.5 cm H₂O are best avoided because of the detrimental effects on cardiac output, regional blood flow, and possible barotrauma with lung injury (34). Frequent arterial blood gas measurements with appropriate ventilatory adjustments and good pulmonary toilet are essential. The FI_{O2} should be increased to 100% immediately before donor surgery and transport to the operating room. The only exception is during heart-lungs retrieval where an F_{I_o} , of <40%, a normal tidal volume (10-12 mL/kg), and a peak inspiratory pressure <30 cm H₂O should be maintained to minimize the possible effects of oxygen toxicity and pressure injury to the lungs.

Diabetes Insipidus

Diabetes insipidus, which may complicate even minor cases of head injury, is a frequent occurrence in brain-dead patients (35,36). Pituitary or hypothalamic dysfunction with lack of central secretion of antidiuretic hormone will result in an inappropriate, frequently massive urine output that bears no relationship to the intravascular fluid volume. If not properly treated, DI will result in serum hyperosmolality, hypernatremia, hypermagnesemia, hypokalemia, hypophosphatemia, and hypocalcemia (37). Hemodynamic instability will occur secondary to hypovolemia or electrolyte imbalances. As polyuria may be multifactorial, titration of urine output and free water clearance against the serum electrolytes, serum blood glucose, and intravenous infusions is essential. Fluids are administered in the form of colloid or electrolyte solutions, preferably as a hypotonic solution such as half normal saline or dextrose in water, in an amount sufficient to replace urinary losses, meet daily fluid requirements, and maintain the serum sodium at <155 mEq/L. Serum electrolytes and osmolality should be monitored every 4-6 h. Twenty milliequivalents of potassium chloride or potassium phosphate is added to each liter of intravenous solution given, with additional supplements as required to maintain the serum potassium level above 3.5 mEq/L.

In severe cases of central DI, where the urine output exceeds 1000 mL/h and inotropic support becomes necessary to sustain a satisfactory arterial pressure, titration of a controlled intravenous infusion of vasopressin starting at 0.1 U/min or 2-10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or of 0.3 $\mu g/kg$ desmopressin acetate to maintain a urine output of 100-200 mL/h (1.5-3 $mL \cdot kg^{-1} \cdot h^{-1}$) may be efficacious (38). Intramuscular or subcutaneous administration is discouraged as absorption may be variable, depending on the donor's core temperature and adequacy of cutaneous and skeletal muscle perfusion. Early intervention is best as persistent polyuria may wash out the renal medullary concentration gradient, reducing the kidney's responsiveness to vasopressin. This will necessitate the infusion of higher doses to achieve a desired antidiuretic effect with the concomitant concern of causing ischemic injury to transplantable organs.

The use of vasopressin to limit the morbidity of polyuria and hemodynamic instability in a brain-dead organ donor is a controversial subject. The hemodynamic effects of vasopressin are dose-dependent and include generalized systemic vasoconstriction with an increase in blood pressure and a decrease in cardiac output, coronary and renal blood flow, bradycardia, and arrhythmias (39). Nitroprusside and nitroglycerin administration may minimize the undesirable cardiovascular and renal side effects of vasopressin, but may also result in a deterioration in gas exchange from an increase in the intrapulmonary physiologic shunt (40,41). Schneider and associates reported that kidneys obtained from donors supported with dopamine and/or pitressin demonstrated a higher incidence of acute tubular necrosis and lower rate of graft survival (42). Support for the use of vasopressin as a continuous infusion is provided by the work of Blaine and associates in a brain-dead porcine model. They reported physiologic levels of vasopressin, with normal plasma osmolarity and serum sodium, a decrease in urine output, potassium, and fluid requirements, and no effect on the peripheral vascular resistance or microscopic evidence of organ ischemia (43).

With currently available information, it appears that the benefits of early treatment of the polyuria of DI with a titratable infusion of vasopressin, thereby minimizing electrolyte abnormalities, fluid shifts, and a reduction in core temperature, outweigh the potential for ischemic end-organ injury.

In the absence of DI, renal management should be based on optimizing filling pressures while monitoring the central venous pressure. If the patient is well hydrated, with a central venous pressure between 8 and 12 cm $\rm H_2O$, and the urine output is inadequate, the use of mannitol, furosemide, or dopamine at 2–5 $\mu \rm g \cdot k g^{-1} \cdot min^{-1}$ may enhance renal function as well as provide protection from preservation injury.

The use of large volumes of dextrose-containing crystalloid, α -agonist vasopressors, catecholamines, or glucocorticoids may predispose to a hyperglycemic, hyperosmolar state and subsequent intracellular dehydration, osmotic diuresis, or worsening of increased intracranial pressure, metabolic acidosis, and ketosis. Serum glucose, potassium, and ketones must be monitored, and an insulin infusion must be used to maintain the serum glucose level between 5 and 9 mmol/L.

Sepsis

Avoiding infection with vigorous sterile techniques is essential in catheter, tracheobronchial, and wound care. Donors with systemic bacterial infections treated with a suitable wide-spectrum nonnephrotoxic antibiotic according to known antibiotic sensitivities are still suitable if the infection is eradicated before actual donation. Centers may routinely administer antibiotic prophylaxis to prevent transmission of an infectious agent to the immunosuppressed recipient. Surveillance for infection includes monitoring the pulmonary status with daily chest x-rays, sputum cultures and sensitivities, urine and blood cultures, and serologic screening for syphilis, hepatitis B, human immunodeficiency virus, and cytomegalovirus.

Hypothermia

Because of the loss of hypothalamic temperature regulation, brain-dead donors are poikilothermic and may need very aggressive warming to maintain a core temperature above 34°C. Although a mild degree of hypothermia may be beneficial to organ protection and preservation, a core temperature <32°C could

result in dysrhythmias, cardiovascular instability, a decrease in glomerular filtration rate and cold diuresis, coagulopathy, a left shift in the oxyhemoglobin dissociation curve, and pancreatitis (44). Hypothermia further complicates the process of certification of brain death. Therapeutic intervention should be early and vigorous (45,46).

Anemia and Coagulopathy

An adequate flow of oxygenated blood to organs for transplantation depends on arterial oxygen content, cardiac output, and regional distribution of blood flow. Donors are usually transfused with packed red blood cells in the intensive care unit to maintain the hematocrit at $\geq 30\%$ (47). The efficacy of this practice is debatable but supported by the application of basic science principles in attempting to maximize cellular oxygenation. The effect of circulating volume in augmenting cardiac output is more important than the effect of the hemoglobin level or viscosity of blood in oxygen transport (48). Hypervolemia may predispose to donor organ edema, and therefore oxygen delivery in a normovolemic patient may be best achieved by maintaining the hematocrit between 30% and 45% (49). The risks of blood-product use include the possibility of transmitting infectious diseases, electrolyte disturbances, transfusion reactions, and some difficulty with matching histocompatibility.

A bleeding diathesis may be initiated by the release of tissue fibrinolytic agents or plasminogen activators from a necrotic brain into the systemic circulation (50,51). Despite factor replacement, primary fibrinolysis or disseminated intravascular coagulation may persist, necessitating early organ retrieval. The use of ε -aminocaproic acid is not recommended as microvascular thrombosis may be induced in the donor organs, causing subsequent donor graft failure.

Endocrine Abnormalities

It has recently been proposed that brain death may interrupt hypothalamic and pituitary axis function. Consequently, hypothyroidism or adrenal insufficiency may in many organs lead to functional instability from intracellular depletion or abnormal mitochondrial regeneration of adenosine triphosphate. Novitzky et al., in brain-dead animal models, found a progressive reduction in circulating cortisol, insulin, and free triiodothyronine (T_3) (52). A similar reduction in free T_3 and thyroxine (T_4) has been found in

human organ donors (53,54). A need for increased mean dosage and duration of inotropic support to maintain an adequate arterial blood pressure has been recorded in patients receiving hearts from thyroid-hormone-depleted donors (55). In addition, it has been claimed that therapy with T_3 in human donors offsets the natural course of deterioration of the brain-dead patient and improves cardiac and renal functional stability in the recipient (56). It has been suggested that these acute biochemical changes in thyroid hormone values (normal T_4 , low free T_3 , and normal rT₃) may represent a sick euthyroid syndrome with a decreased production or normal metabolic clearance of rT₃, an inactive form of T₃ generated through an alternate pathway of T₄ metabolism (57,58). A low free T_3 or cortisol level was not found to be predictive of the need for inotropic support (57). The beneficial effects reported for T_3 replacement therapy (i.e., conversion of anaerobic to aerobic metabolism with improved organ function) (59) may represent a pharmacologic effect independent of the actual physiologic status of the donor.

Care of the donor can be time-consuming and emotionally draining on the resources of a critical care unit; it should be undertaken, however, with the same vigilance and dedication that one would exercise for any patient in an intensive care setting. The therapeutic goals for optimum perioperative management are simple and can be summarized as follows: Rule of 100s: maintain systolic blood pressure >100 mm Hg, urine output >100 mL/h, Pao₂ >100 mm Hg, and hemoglobin >100 g/L (60).

Donor Management in the Operating Room

Declaration of brain death is made before transporting the donor patient to the operating room. The anesthesiologist should verify the appropriate medical and legal documentation of family consent for organ donation and certification of death. When the donor is to be transferred to the transplant center for organ retrieval, the brain-death criteria of the second hospital must be met. Intensive care management continues intraoperatively with an emphasis on optimum organ perfusion and oxygenation.

Monitoring of the electrocardiogram, central venous pressure, urine volume, core temperature, breath sounds, capillary oxygen saturation, and endtidal CO₂ is essential, as is placement of an arterial catheter in an upper extremity to facilitate sampling and monitoring of the arterial blood pressure during sequential organ removal. The use of a pulmonary

artery catheter is seldom necessary for the assessment of intravascular volume status and has been reported to cause right-sided endocardial lesions (61). Arterial blood gas tensions, acid-base status, hematocrit, electrolytes, and blood glucose should be measured every hour.

Ventilatory requirements include maintaining adequate oxygenation, avoiding atelectasis, barotrauma, and oxygen toxicity (heart-lungs), and minimizing disruption of the surgical field and heat loss. Ventilatory settings include an Fio, of 1 (lungs or heart-lungs transplant $F_{I_{O_2}} = 0.4$) while maintaining a Pao₂ of 75–150 mm Hg, PEEP \leq 7.5 cm H₂O, tidal volume 10-12 mL/kg, and a rate adjusted to maintain a Pco₂ of 35-45 mm Hg. Clearly, with a decrease in oxygen consumption and carbon dioxide production, normal ventilatory support will result in a respiratory alkalosis. Theoretically using the en-block, "notouch" procurement technique, while maintaining a Paco₂ of \geq 45 mm Hg, may optimize organ perfusion by avoiding iatrogenic arterial vasospasm, a direct vasodilatory effect of hypercapnia, and an increase in cardiac output, resulting from stimulation of the sympathetic nervous system. Mild hypercapnia (Paco₂ = 59 mm Hg) increases portal vein blood flow and total hepatic blood flow but also causes a concomitant reduction in hepatic function. The question of whether hemodynamic responses to alterations of Paco₂ parallel changes in end-organ function has been raised (62,63).

To avoid reflex neuromuscular activity and to facilitate surgical exposure, 0.15 mg/kg of pancuronium is given intravenously. Although declaration of brain death requires the loss of cerebral and brainstem reflexes, spinal reflexes remain intact. Complex movements of the limbs and trunk can be confused with reflex movements of cerebral origin and may create tremendous anxiety for operating-room personnel (64,65).

A reflex pressor response to nociceptive stimuli in brain-dead patients, one that may lead to excessive operative blood loss and damage to the renal grafts, has been well described (66). Management requires venodilation and/or a reduction in afterload, while minimizing any possible adverse drug toxicity, especially to the liver and kidneys. Therefore nitroglycerin or nitroprusside may be the best choice of agents, although isoflurane is usually the closest at hand.

For hemodynamic stabilization, the first step involves fluid resuscitation with crystalloid, colloid, or albumin, using the filling pressures, heart rate, and possibly cardiac output and mixed venous oxygen saturation for therapeutic end-points. Guidelines for maintaining cardiovascular homeostasis will vary at

the discretion of the individual anesthesiologist, but in general most institutions consider acceptable a central venous pressure of 8–12 cm H₂O, pulmonary capillary wedge pressure of 10 ± 3 mm Hg, a mean pulmonary arterial pressure of 15 ± 4 mm Hg, cardiac output of 4-8 L/min, and mixed venous saturation >75%. The choice of inotropes in order of preference include dopamine at a maximum of $10 \,\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, dobutamine at a maximum of 15 μ g·kg⁻¹·min⁻¹, epinephrine at $\leq 0.1 \ \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and, in dire straits, norepinephrine with dopamine for renal protection. Intraoperative use of dopamine may be desirable at low doses (2–5 μ g·kg⁻¹·min⁻¹) to promote renal vasodilation, to increase renal blood flow, glomerular filtration rate, and urine output, and for pressure support at 5-7 μ g·kg⁻¹·min⁻¹ with lung retraction and cardiac manipulation during heart-lungs procurement. Again the use of pure α -agonist vasopressor agents is discouraged. In addition to adjusting preload, afterload, and contractility, a normal heart rate and rhythm is important. Other possible causes of perioperative hypotension should be considered, including raised intracranial pressure with cerebellar tonsillar herniation and acute C₁ spinal cord shock, rapid infusion of preservation solution into the portal system with precipitous hypothermia and cardiovascular instability, or cardiorespiratory changes inherent in the surgical technique of organ recovery (including sternotomy, manipulation of the heart, and intraperitoneal dissection of the inferior vena cava). Even with the most rigorous efforts, the inevitable deterioration of the brain-dead patient will lead to cardiovascular

In the event of cardiac arrest, cardiopulmonary resuscitation should be started to maintain an effective circulation. Procurement of liver and kidneys should proceed rapidly with cross-clamping of the aorta at the diaphragm and infusion of cold preservation solution into the distal aorta and portal vein.

Causes of anemia include hemorrhage, surgical blood loss, and hemodilution. Infusion of packed red blood cells to keep the hematocrit >30% facilitates a satisfactory oxygen-carrying capacity and cardiovascular integrity. Recently various groups have reported that immunization of the donor can improve heterotopic graft survival in recipient animal models (67). The mechanism of this donor transfusion effect is not clear.

Pharmacologic intervention has frequently been used to improve the viability of the kidneys before transplantation. Commonly used agents are dopamine, mannitol (1 g/kg), furosemide (40–100 mg), and thorazine. After aortic cannulation and before occlusion of the proximal aorta, 20,000 U of heparin (300

U/kg in children) is administered intravenously. Cold potassium cardioplegia should be available for infusion.

Anesthetic support of the organ donor is necessary until surgical occlusion of the proximal aorta and start of in situ flushing of organs, after which all monitoring and supportive measures must be discontinued. This limits the amount of emotional distress for operating-room personnel involved in witnessing the slow anoxic cardiac death of a donor if only the kidneys and liver are being retrieved. A record should be kept of the time of cross-clamp of the proximal aorta, and of infusion of cardioplegia solution, as the starting point of cold ischemia time for the transplantable organs.

Donor Operation

Multiple organ retrieval from a cadaveric donor is a sterile procedure lasting approximately 3–4 h. The procurement team usually consists of one or more visiting surgical groups and transplant coordinators who work in concert with the donor-institution operating team of surgeons, nurses, and anesthesiologists. Anesthetic support of the organ donor is necessary until surgical occlusion of the proximal aorta and the start of in situ flushing of organs with preservation solution, after which the ventilation, monitoring, and intravenous infusions are discontinued.

There has been a gradual evolution of surgical techniques from meticulous in vivo dissection and skeletonization of individual vessels with removal of warm organs to the modern techniques of "notouch," en bloc procurement and in situ core cooling of organs (68,69). Theoretically, these two principles minimize ischemic injury from surgically induced arterial vasospasm with subsequent uneven flushing and cooling of the donor organ.

With positioning and surgical preparation of the donor, a complete midline incision from the suprasternal notch to pubis is made, and the sternum is split.

The supporting ligaments of the liver are divided, an incision is made in the crux of the diaphragm, and the supraceliac aorta is encircled with an umbilical tape. The inferior mesenteric vein is cannulated to allow flushing of the liver through the portal system, and a second ligature is placed around the aorta at the level of the inferior mesenteric artery to allow for cannulation and aortic perfusion. The heart or heartlungs team then prepares their organ(s) for removal. For donor heart excision, the pericardium is incised

and the heart examined for any abnormal structures or dyskinetic segments. The aorta and superior vena cava are freed from the right pulmonary artery, and the azygous vein is ligated and divided. With administration of 20,000 U or 300 U/kg of heparin, the cardioplegia catheter is inserted into the ascending aorta, the distal aorta is ligated, and an aortic perfusion cannula is inserted. The central venous catheter is withdrawn and with inflow occlusion of the superior vena cava and cross-clamping of the aorta just proximal to the innominate artery and at the diaphragm, a cardioplegia solution for cardiac perfusion, lung preservation solution for pulmonary flushing, and a cold flush solution of lactated Ringer's, Eurocollins, or Belzar's solution for the kidneys and gastrointestinal organ(s) are started simultaneously. Outflow for the perfusate is provided by dividing the inferior vena cava at the level of the diaphragm or near its abdominal bifurcation to prevent venous hypertension with congestion of the liver and kidneys; the sequential removal of organs then proceeds. Spleen and omental lymph nodes are removed for tissue typing, and aorta, inferior vena cava, and iliac vessels are removed for later use as vascular grafts.

Kidneys may be preserved for up to 72 h, but they seldom do well in the recipient after 36–48 h; the heart and lungs should be transplanted within 3–4 h, and the pancreas probably within 6 h. A new preservation solution recently introduced from the University of Wisconsin has allowed an extension of the safe cold-preservation time for the liver from 8 to 24 h (70).

The technique of heart-lungs procurement merits special attention. Positioning of the endotracheal tube should be confirmed with the heart-lungs transplant surgeons so as to minimize mucosal injury in the trachea where the suture line will occur. Division of the mediastinal pleura and dissection of the trachea from attachments to the aorta and esophagus with manipulation of each lung separately out of the mediastinum results in significant mechanical hypotension and difficulties with ventilation and oxygenation. Dopamine (5–7 μ g·kg⁻¹·min⁻¹) may be required for cardiovascular support with an acceptable minimum mean arterial pressure of 60 mm Hg during this interval of manipulation. With insertion of the cardioplegia catheter into the root of the aorta, a double cannula is placed in the main pulmonary artery for hypothermic flushing via the right and left pulmonary arteries. After the infusion of potassium cardioplegia solution to the heart, the lung flush is started and the lungs are manually ventilated with 4 breaths/min. If prostaglandin E1 is contained in the

preservation solution or infused systemically, one may anticipate profound hypotension. When ventilatory support is discontinued, the airway is suctioned and the endotracheal tube removed. With division of the superior vena cava and trachea, the heart and lungs are removed from the chest. The aorta and inferior vena cava are then stapled closed, and the end of the trachea is wrapped in Betadine-soaked gauze.

After hypothermic perfusion with a preservation solution, the donor organs are stored in plastic coolers in iced preservation solution.

Organ Preservation

Traditionally, optimal organ preservation has been achieved by the combination of maximizing donor hemodynamics, improved surgical procurement techniques with rapid in situ core cooling, and cold storage techniques with a hyperkalemic, hyperosmolar solution. Many centers use donor-directed experimental therapeutic modalities in an attempt to improve donor organ function.

Iced storage and core cooling result in a slowing of cellular metabolism and energy consumption. Donor heparinization prevents microvascular thrombosis, promoting even flushing and eventual reperfusion. The use of hypertonic solutions or impermeates suppresses the cell swelling that is induced by hypothermia. Pharmacologic manipulation in the donor may include allopurinol (free radical scavenger), chlorpromazine (vasodilation), and prostaglandin E₁ (vasodilation, membrane stabilization, antiplatelet effect). There is some evidence that the administration of steroids leads to improved kidney and heart protection against ischemic injury. Methylprednisolone (30 mg/kg) is routinely administered at least 2 h before excision of the donor organs (71,72).

Summary

Organ transplantation is a multidisciplinary specialty that has seen remarkable advances in the past two decades, in the tireless pursuit of providing lifesaving therapy for patients suffering from end-stage organ failure. As the scientific basis and clinical practice of organ transplantation continues to evolve, it becomes increasingly apparent that "what was inconceivable yesterday, and barely achievable today, becomes routine tomorrow" (73).

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Clinical Reports

Alfentanil and Delayed Respiratory Depression: Case Studies and Review

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Key Words: ANALGESICS, ALFENTANIL—respiratory depression.

Several reports describing severe delayed respiratory depression after alfentanil anesthesia have appeared in the literature (1–7). Lamarche et al. reported one case of respiratory arrest 40 min after admission to the recovery room (1). Sebel et al. reported two cases of respiratory arrest occurring 63 and 70 min after discontinuation of alfentanil infusions (3). In those two cases, full consciousness and adequate reversal of neuromuscular blockade were documented before respiratory arrest, and both responded to naloxone. Raeder and Hole, investigating various dosage schedules for alfentanil, reported five instances of respiratory arrest occurring 20-45 min after the completion of anesthesia (4). Three additional case reports, involving four patients with severe respiratory depression after alfentanil, have been published (5–7).

During a 15-mo period at our institution, three cases of severe delayed respiratory depression were encountered. We now report these three cases and review possible etiologic mechanisms.

Case 1

A 53-yr-old, 73-kg woman with lumbosacral and right leg pain was scheduled for L4-5 discectomy. Past medical history was negative except for a 15 pack-

year smoking history; physical examination and preoperative laboratory evaluation were unremarkable. Morphine (7 mg intramuscularly) was given preoperatively.

After preoxygenation, general anesthesia was induced intravenously with 100 µg/kg alfentanil, 5 mg midazolam, and 50 mg atracurium. Four milliliters of 4% lidocaine was given laryngotracheally, and an orotracheal intubation was performed. Anesthesia was maintained with a $1-\mu g \cdot kg^{-1} \cdot min^{-1}$ alfentanil infusion and 67% N_2O , with an additional 7.5- μ g/kg alfentanil bolus given just before the surgical incision. Droperidol (2.5 mg intravenously) was also given. Vital signs remained stable except for one brief period of mild hypertension, which responded to 0.3%-0.5% isoflurane. The alfentanil infusion was discontinued 30 min before the end of surgery; the total alfentanil dose, 18.8 mg, was given over 150 min for an average of 1.7 μ g·kg⁻¹·min⁻¹. At the completion of the case, 0.35 mg naloxone was given intravenously, and the patient was extubated.

Initial vital signs in the recovery room with the patient alert and breathing comfortably were heart rate, 80 beats/min; blood pressure, 140/90 mm Hg; and respiratory rate, 12 breaths/min. One hour and 40 min after discontinuation of the alfentanil infusion, she was found apneic and unresponsive. Mask ventilation with 100% O₂ was immediately begun, and 0.14 mg naloxone was given intravenously in divided doses. The patient regained consciousness and remained stable until 75 min later when her respiratory rate slowed to 6 breaths/min. The patient was then given 0.1 mg naloxone intravenously. The remainder of the patient's hospital course was uneventful, and she was discharged on the fourth postoperative day.

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Case 2

A 58-yr-old, 52-kg man with a tongue lesion was scheduled for direct laryngoscopy, nasopharyngoscopy, esophagoscopy, and biopsy on an outpatient basis. Past medical history was notable for hypertension treated with metoprolol, slight dyspnea on exertion, and a 40 pack-year smoking history. Physical examination was unremarkable except for the tongue lesion, and preoperative laboratory values were normal. Pulmonary function tests included an FEV₁ of 1.94 L and an FVC of 3.67 L. No preoperative medications were given.

After preoxygenation, general anesthesia was induced intravenously with 50 μ g/kg alfentanil, 250 mg sodium thiopental, 2 mg midazolam, and 6 mg vecuronium, followed by orotracheal intubation. Mild hypotension after induction was treated with a rapid intravenous fluid infusion and 15 mg ephedrine intravenously, with stable vital signs thereafter. Anesthesia was maintained with a 0.75–1.0 μ g·kg⁻¹·min⁻¹ alfentanil infusion and 70% N₂O. The alfentanil infusion was discontinued 5 min before the end of surgery, with the total alfentanil dose of 4.63 mg administered over 44 min for an average of 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At the completion of surgery, 0.12 mg naloxone, 2.5 mg neostigmine, and 0.5 mg glycopyrrolate were given intravenously. Neuromuscular blockade reversal was documented by nerve stimulator and clinical criteria, and the patient was extubated.

On arrival in the recovery room, the patient was awake, alert, and breathing well, with a heart rate of 84 beats/min, blood pressure 160/90 mm Hg, and respiratory rate 24 breaths/min. Fifteen minutes later (35 min after discontinuation of alfentanil), he was noted to be pale with shallow respirations; Sao₂ while breathing 40% O₂ by mask rapidly decreased to 70%. Naloxone (0.12 mg intravenously) was given, but nasal intubation was required before the effect could be fully seen. The patient was extubated several hours later, observed overnight, and then discharged in good condition the next morning.

Case 3

A 30-yr-old, 55-kg woman with secondary infertility was scheduled for diagnostic hysteroscopy and laparoscopy on an outpatient basis. Past medical history was notable only for mild asthma, and physical examination and preoperative laboratory evaluation were unremarkable. No preoperative medications were given.

<u>Table 1</u>. Summary of Data From Three Cases of Delayed Respiratory Depression After Alfentanil Anesthesia

	Case 1	Case 2	Case 3
Initial bolus dose of alfentanil (µg/kg)	100	50	50
Initial alfentanil infusion rate (μg·kg ⁻¹ ·min ⁻¹)	1.0	0.75	1.0
Duration of surgery (min)	125	35	60
Duration of alfentanil infusion (min)	150	44	62
Total alfentanil dose (mg)	18.8	4.63	6.75
Average alfentanil dose (μg·kg ⁻¹ ·min ⁻¹)	1.7	2.0	2.0
Time from end of alfentanil infusion to respiratory arrest (or reintubation) (min)	100	35	31

After preoxygenation, general anesthesia was induced intravenously with 50 μ g/kg alfentanil, 150 mg sodium thiopental, 1.25 mg droperidol, and 7 mg vecuronium. After orotracheal intubation, anesthesia was maintained with a $1-\mu g \cdot k g^{-1} \cdot min^{-1}$ alfentanil infusion and 70% N_2O_1 , with an additional 7.5- μ g/kg alfentanil bolus given during the case. Vital signs remained stable, and the alfentanil infusion was discontinued 15 min before the end of surgery. The total dose of alfentanil was 6.75 mg administered over 62 min for an average of 2.0 μ g·kg⁻¹·min⁻¹. At the completion of the case, 2.5 mg neostigmine and 0.5 mg glycopyrrolate were given intravenously. Neuromuscular blockade reversal was documented by nerve stimulator and clinical criteria, and the patient was extubated.

On arrival in the recovery room, the patient was drowsy but easily arousable, with vital signs of heart rate 88 beats/min, blood pressure 112/80 mm Hg, and respiratory rate 14 breaths/min. Thirty-one minutes after discontinuation of the alfentanil infusion, she was noted to be apneic, and her carotid pulse was not palpable. Chest compressions and mask ventilation with 100% $\rm O_2$ were immediately begun, and 1 mg atropine and 0.4 mg naloxone were given intravenously. Within 30 s, the patient regained consciousness and resuscitation was discontinued. She was observed overnight and discharged in good condition the next day. See summary of data in Table 1.

Discussion

Including our cases, there are now at least 15 reported instances of severe, potentially life-threatening, delayed respiratory depression after alfentanil anesthesia. In most of these cases it was documented

that the patients were awake and breathing spontaneously on arrival in the recovery room and that neuromuscular blockade was adequately reversed before extubation. Rapid resumption of spontaneous respiration after naloxone opioid antagonism, given after the onset of respiratory depression, was also documented in most cases.

Alfentanil is thought by some to have advantages over other opioids, such as fentanyl, because of its pharmacokinetic properties. Camu et al. reported a rapid distribution of alfentanil best fitting a threecompartment model, with a tug of 94 min, a volume of distribution of 1.03 L/kg, and a clearance of 456 mL/min (8). Others have noted similar findings (5,9– 22), although some support a two-compartment model (18,22). Alfentanil has a smaller volume of distribution, lower clearance, and shorter elimination half-life than fentanyl (8,11,14). It has less tissue accumulation than fentanyl because of its lower lipid solubility and greater plasma protein binding (8,23-25). The rapid onset of alfentanil is a result of a low pKa so that nearly 90% of the drug exists in the nonionized form at a physiologic pH. It is the nonionized fraction that readily crosses the blood-brain barrier. There should also be a good correlation of effect and plasma concentration, as well as a short duration of effect. Alfentanil would be expected to be a good drug for surgery where immediate extubation postoperatively is planned.

The cause of delayed respiratory depression after alfentanil anesthesia is unknown, but many factors can be implicated. Large doses resulting in high plasma levels at the time of extubation, despite the rapid distribution and elimination of alfentanil, is one postulated mechanism. Hull (26) points out that of the five cases of respiratory arrest reported by Raeder and Hole (4), two patients had received a relatively large total dose of alfentanil (about 4 μ g·kg⁻¹·min⁻¹). High plasma levels at extubation would be expected in those patients, but they were initially awake, alert, and breathing spontaneously. Among the other 10 reported in the literature, the next largest alfentanil dose was 2.73 μ g·kg⁻¹·min⁻¹, and most were below $2 \mu g \cdot kg^{-1} \cdot min^{-1}$. Those doses are similar to the ones commonly used by practitioners planning early extubation at the completion of surgery. In the two cases in which alfentanil plasma concentrations were measured, one patient had a relatively high level of 610 ng/mL at extubation and 210 ng/mL at the time of respiratory depression (5), the other a level of 87 ng/mL at the time of respiratory arrest (6). Using a computer program described by Maitre et al. (21), Jaffe and Coalson (7) estimated an alfentanil level of 63 ng/mL at the time of apnea in their patient.

Most of these levels are below the threshold for resumption of spontaneous respiration (100–240 ng/mL) (7,9,21,27,28). As with other opioids, however, respiratory depression due to alfentanil can occur at plasma concentrations lower than this threshold. Sensitive measures such as the slope of the CO₂ response curve have demonstrated respiratory depression at plasma alfentanil levels of 20.8 ng/mL (29) and 23.9 ng/mL (30).

Another factor complicating the issue of optimal dosing of alfentanil is its potency relative to other opioids. Potency, when calculated on the basis of dose of alfentanil, has been reported as 3:1 (alfentanil/fentanyl) (15), but most studies suggest a ratio ranging from 6:1 to 10:1 (11,29,31,32). The potency ratio based on plasma concentrations has been reported as 40:1 (alfentanil/fentanyl) (16,29). A recent pharmacodynamic study comparing effects of opioids revealed a plasma potency ratio of 75:1 (alfentanil/fentanyl) based on spectral edge electroencephalographic data (33).

Interindividual variability in alfentanil pharmacokinetics could result in unexpectedly high plasma levels in some patients, causing respiratory depression (5,17,18,21,22). McDonnell et al. (18) reported one patient with a $t_{\nu_2 \beta}$ of 151 min, and Reitz et al. (5) described two patients with t₁₂₈ values of 182 and 213 min. Bovill et al., in a study of 10 patients, found the mean alfentanil half-life to be 304 min (13). Obesity has been shown to affect the pharmacokinetics of alfentanil. Bentley et al. reported a tize of 172 min in obese patients compared with 92 min in a nonobese control group with associated decreased clearance rates (179 and 321 mL/min, respectively) (19). The pharmacokinetics of alfentanil are also altered by age. Clearance and elimination of alfentanil decrease with increasing age in adults, and dosage reductions up to one-third are recommended in older patients (2,21,22,34). Reitz et al. noted that in a case of delayed respiratory depression that they encountered, surgery was lengthy (5). They raised the question of whether decreased hepatic blood flow, known to occur after prolonged surgery, could cause unusually high plasma levels of alfentanil. They also postulated the release of alfentanil postoperatively from muscles after motor activity and muscle tone had resumed. Finally, the protein-binding properties of alfentanil might lead to pharmacokinetic variability. Unlike fentanyl, which is primarily bound to plasma albumin and lipoproteins (17,35), alfentanil is mainly bound to α_1 -acid glycoprotein. This may be a cause of interindividual and intraindividual variability, especially during periods of stress or pregnancy.

Studies have shown that fentanyl may be associ-

ated with secondary peaks in plasma concentration (36,37). Several authors have also demonstrated secondary peaks in alfentanil plasma concentration, occurring 20-360 min after discontinuation of the drug (5,12,18,36). One possible explanation for this is enterosystemic recirculation, also known as gastric trapping or pH trapping. In a very acidic environment, such as the stomach, the fraction of the ionized form of a basic drug is increased. The stomach can sequester the poorly permeable ionized drug and release it at a later time when it may be reabsorbed in its nonionized form in the less acidic small intestine. The role of gastric trapping of alfentanil has been considered by several authors (5,17,26,38), but few if any investigations of this phenomenon with alfentanil have been carried out.

In all of the reported cases of delayed respiratory depression after alfentanil, other drugs were given concomitantly. Two classes of drugs come readily to mind as possible contributors to respiratory depression, the benzodiazepines and muscle relaxants. The combination of diazepam and alfentanil has been shown to cause greater respiratory depression (and even apnea) than alfentanil alone (39). Sleep may potentiate this effect. Muscle relaxants were given in virtually all of the 15 cases of delayed respiratory depression that were reviewed; however, adequate reversal was documented in most cases.

Naloxone was given to some of the 15 reported patients who experienced delayed respiratory depression after alfentanil either at the time of extubation or later when respiratory depression occurred. A few of the patients required repeated doses. This is consistent with the relatively short duration of effect of naloxone (26,38). The role of naloxone in delayed respiratory depression after alfentanil is unclear.

In conclusion, because of its pharmacokinetic properties many believe that alfentanil should be a useful drug for those cases in which prompt extubation after surgery is planned. There have, however, been multiple reports of severe delayed respiratory depression after alfentanil administration. The incidence of this complication is unknown. Many pharmacokinetic, pharmacodynamic, and clinical factors have been implicated as possible contributors to this problem. To decrease the possibility of delayed respiratory depression, the dose of alfentanil should be carefully titrated and appropriately adjusted in patients in whom reduced requirements can be anticipated. In the recovery room, oxygen administration and oxygen saturation monitoring should be routine, with naloxone always immediately available. Recovery room personnel need to be made aware of the potential for delayed respiratory depression after alfentanil anesthesia, even in the initially alert, spontaneously breathing patient.

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Percutaneous Pulmonary Artery Catheterization in Pediatric Cardiovascular Anesthesia: Insertion Techniques and Use

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Key Words: ANESTHESIA, PEDIATRIC—cardiac surgery. MONITORING, PEDIATRIC—pulmonary catheters.

Pediatric patients having corrective surgery for congenital heart defects are often difficult to manage during the first 24-48 postoperative hours. Perioperative cardiovascular instability results from several factors including the pathophysiology resulting from the primary anatomic defect, hemodynamic effects of anesthetic drugs and ventilation techniques, inadequate myocardial preservation during cardiopulmonary bypass, damage to the myocardium as a result of the surgical repair, and pulmonary vasomotor instability secondary to extracorporeal circulation. Monitoring of cardiovascular function by pulmonary artery (PA) catheterization during the critical postoperative period can guide appropriate therapeutic interventions. It is well established that the knowledge of cardiac output is helpful in making appropriate patient-care decisions after cardiac surgery (1). Damen and Wever (2) reported that data obtained with PA catheters prompted critical therapeutic interventions in 35% of 58 children undergoing cardiac surgery.

Despite the common use by anesthesiologists of the flow-directed thermodilution PA catheter in adult cardiac surgery, its utilization in pediatric congenital heart surgery is infrequent. A number of reasons may contribute to this infrequent use, including difficulty in gaining central venous access, inexperience in catheter placement, concerns as to potential complications, and questions about the accuracy of the data obtained.

Few technical guidelines for insertion of PA cath-

eters in children have been described in the literature. Tuggle et al. (3) demonstrated the need to use techniques in addition to waveform analysis that assist in successful placement of these catheters in small children. Through the use of fluoroscopy, we have developed a reliable and efficient method of percutaneously placing PA catheters in pediatric patients in the operating room. The data obtained by the use of these catheters were helpful in guiding therapeutic interventions both intraoperatively and postoperatively. This report describes an 18-mo experience with percutaneously inserted thermodilution PA catheters in 54 children undergoing surgical correction of various congenital heart defects.

Methods

Children were selected as candidates for catheterization (see Discussion for criteria) according to body size (Table 1) and procedure (Table 2). Proper catheter size was determined by examination of a recent chest x-ray. The projected catheter position in the cardiac shadow provided a reliable estimate of the necessary distance between the proximal and distal ports. For monitoring of central venous pressure (CVP), the proximal port should be located in the area of the atrium when the catheter tip (distal port) is in its final PA position. In children weighing less than 18 kg, we used a 5F, 7.5- or 10-cm sheath introducer (501-615S, Cordis Corporation, Miami, Fla.) with a 4F thermodilution PA catheter (JX 30B/AI-07173, Arrow International, Reading, Pa.). This PA catheter is 75 cm long and has the CVP port located 10 cm proximal to the tip. In children weighing more than 18-20 kg, we used a 6F, 10-cm sheath introducer (AK-09601, Arrow International) with a 5F thermodilution PA catheter (93A-105-5F, American Edwards Laboratories, American Hospital Supply Corporation, Irvine, Calif.; and SP5105HPN 140251-053-000, Spectramed, Oxnard, Calif.), which was also 75 cm in length, but

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Table 1. Patient Age and Size Distribution

Age (yr)	No. of patients	Weight (kg)*	Height (cm)*
<1	8	5.2	56.5
1–2	1 4	10.0	78.0
>2-5	15	15.3	98.0
>5	17	27.0	130.0

Mean values.

with an optional location of the CVP port at either 10 or 15 cm proximal to the tip.

Our first choice for catheter insertion was via the external jugular vein, but our success at entering the central circulation from this site was unpredictable, particularly in patients weighing less than 10 kg. The internal jugular and the femoral veins were second choices. Regardless of the route of insertion, fluoroscopy was used to guide the catheter tip into the atrium. If the anatomy was favorable (see Discussion), the tip was advanced into the right ventricle and then into the PA using both waveform recognition and fluoroscopy. Maneuvering the PA catheter through the heart chambers depended on the ability of the inflated balloon tip to be flow directed, as well as the proper orientation of the balloon tip, which

was accomplished by manual rotation of the external, proximal section of the catheter (4).

Results

No complications were encountered in obtaining central venous access, although additional attempts occasionally were required at more than one insertion site. The femoral vein was used in 41 of the 54 patients. As our experience increased, the ratio of internal jugular to femoral venous insertions also increased. Fluoroscopic guidance assisted catheter placement and decreased insertion times. Insertion times ranged from 5 to 25 min and averaged 12 min from the time of venous cannulation to final catheter placement.

Catheter-related complications included arrhythmias, catheter migration, thrombocytopenia, and thrombosis (Table 2). Catheter insertion was associated with transient supraventricular or ventricular arrhythmias in 70% of our patients. Sudden onset of supraventricular tachycardia occurred in two patients but resolved spontaneously within 1 min of withdrawing the catheter from the atrium. Sustained severe arrhythmias were not a problem and catheter-

Table 2. Patients Monitored With Pulmonary Artery Catheters

Procedure	No. of patients	Age (yr)	PA insertion (time in days)	Complications (No. and type)
VSD repair	14	2.3	2.1 (1–5)	2 TT
*		(0.015-13)	, ,	4 PACT
		, ,		1 TIVC
AV canal repair	5	4.6	4.4	1 PDAM
•		(1.2–16)	(2–7)	1 RVM
				1 PACT
Pulmonary stenosis repair	1	1	2	0
Rastelli	3	6.3	4.3	2 PACT
		(4–10)	(1–10)	
Fontan	8	5.9	5	1 TIVC
		(0.9-13)	(1–7)	
Atrial switch	2	3.3	2	1 TB
		(0.5–6)	(1–3)	
TAPVR repair	1	5	1	0
ToF repair	9	3	3.1	1 PACT
-		(0.9–7)	(2–6)	
Aortic valve repair	5	8.1	1.8	1 PACT
		(5.5–11)	(1–3)	
Mitral valve repair	3	10.6	1	*****
		(9–12)		
Anomalous coronary repair	1	4	1	
ASD (complex) repair	2	4	3	
_			(2-4)	

VSD, ventricular septal defect; AV canal, atrioventricular canal; TAPVR, total anomalous pulmonary venous return; ToF, tetralogy of Fallot; ASD, atrial septal defect; TT, transient tachycardia (insertion); PACT, PA catheter-induced thrombocytopenia; TIVC, thrombosis of the inferior vena cava; PDAM, migration into patent ductus arteriosus; RVM, migration into right ventricle; TB, transient bradycardia (injectate).

Entries for age and PA insertion represent mean values, with the range of values given in parentheses.

induced right bundle branch block (RBBB) was not observed. The catheter was successfully floated from the atrium into the PA in the 32 patients who had favorable cardiac anatomy (see Discussion below).

Catheter migration was observed in two cases, one into a patent ductus arteriosus intraoperatively and one into the right ventricle postoperatively. Migration was diagnosed by acute waveform changes and was easily remedied by catheter withdrawal into a CVP position. The intracardiac presence of a PA catheter during surgical repair was not a technical problem for our surgeons. The catheter was easily retracted when necessary and replaced by the surgeon before closure.

Postoperative thrombocytopenia occurred in 29 of the 54 patients (53%). Thrombocytopenia was defined as a platelet count of less than $100,000/\mu L$ during the postoperative period. This incidence of thrombocytopenia (53%) was not significantly different from the incidence of thrombocytopenia (48%) in another group of patients (57) who had their heart defects surgically treated (primarily atrial septal defect and neonatal repairs) during the same time period without the use of PA catheters but using the same criterion to diagnose thrombocytopenia. In nine patients the thrombocytopenia was resolved within 48 h after removal of the PA catheter. No episodes of catheter-related sepsis were identified.

Routine follow-up cardiac catheterization 1–3 mo postoperatively revealed two patients with asymptomatic narrowing of the femoral vein and inferior vena cava, presumably secondary to catheter-induced venous thrombosis. Both patients were less than 1 yr of age, had been treated for postoperative low cardiac output syndrome, and had the PA catheter (femoral insertion) in place for more than 5 days. In no patient was venous stasis observed during the time the PA catheter was in place.

Discussion

The use of PA catheters in children provides important information about cardiac function during and after congenital heart surgery. At our institution the use of PA catheters in children has become so commonplace that after angiography, if immediate corrective cardiac surgery is planned, our cardiologists will leave the catheter introducer in place (in the femoral vein) for use in the operating room. We have demonstrated that technical skills and use of equipment that are needed to insert these catheters are not beyond the capabilities of anesthesiologists. Operating rooms commonly involved in the care of critically

ill children are usually well-equipped for PA catheterization.

Children selected as candidates for PA catheterization included those with an intact PA or a PA conduit from previous surgery. If the Qp/Qs ratio is ≥ 1 , a flow-directed catheter should advance into the PA with proper manipulation techniques. However, children with simple uncomplicated lesions, e.g., secundum atrial septal defect requiring only a short bypass time for repair, were not considered for PA catheterization. In addition, patients undergoing right heart bypass procedures—such as a modified Fontan operation—that result in direct caval connections to the left and right PAs were not considered as candidates for PA catheters because the divided venous return nullifies the reliability of cardiac outputs determined by thermodilution. The smallest patient in this series weighed 3.2 kg, and three patients weighed less than 4 kg. However, we consider that children weighing less than 5.0 kg are approaching the minimal size for catheterization with the smallest catheter available (4F).

Frequently, children with complex congenital heart disease have some form of right ventricle outflow tract obstruction as a component of their anatomy. Therefore, preoperative placement of the PA catheter into the PA is not possible. Instead, the distal tip of the catheter can be placed in the atrium or, less frequently, in the right ventricle, and during surgery the surgeon can advance the tip of the catheter into the PA before closure of the repair. Because patients with tetralogy of Fallot have an especially high risk of catheter-induced arrhythmias and infundibular spasm, we made no attempts to enter the ventricle or cross the pulmonary outflow tract before repair.

We routinely used fluoroscopic guidance in addition to waveform recognition for placement of PA catheters in pediatric patients. The acute intracardiac angles that must be negotiated to advance these flow-directed catheters through small hearts makes manipulation under fluoroscopy advantageous (5). By visualizing the catheter one is able to avoid entrance into the coronary sinus, left atrium, left ventricle, or pulmonary vein. With fluoroscopy it is possible to see the catheter as it is advanced and avoid both inadvertent entrance into a ventricular septal defect or patent ductus arteriosus and obstruction to a small outflow tract by the inflated balloon.

In adult patients, Damen (6) reported a 68% incidence of transient arrhythmias during insertion and removal of PA catheters. The incidence was the same in our series. Intraatrial manipulations of the PA catheters resulted in sudden supraventricular tachycardia in two of our patients. However, the arrhyth-

mias resolved quickly after temporary withdrawal of the catheter from the atrium. A review of the adult literature revealed a 3%–5% incidence of RBBB associated with PA catheter insertion (7) as well as one reported case of new-onset Wenckebach block (8). We were unable to determine the relative role of the PA catheter in initiating RBBB after surgical repair had been completed because it, too, can result in RBBB.

Swedlow et al. (9) reported in their study that some degree of thrombocytopenia occurred in all eight of their patients after prolonged PA catheterization. Our series of patients showed the incidence of platelet counts below $100,000/\mu L$ to be 53%. This incidence was not significantly different from that seen in pediatric patients undergoing congenital heart surgery without PA catheters (48%). In nine of our patients platelet counts were above $100,000/\mu$ L within 48 h of catheter removal, and four other patients required transfusion with platelets during the catheterization period. We attempt to limit to 48 h the time intravascular catheters are in place, especially in children less than 1 yr of age because the incidence of thrombosis or sepsis may be related to vessel size and duration of cannulation (10). A previous report in adult patients described a 66% incidence of residual thrombosis in the jugular venous system after PA catheterization (11).

The accuracy of thermodilution cardiac output in pediatric patients has been found to be as reliable as any currently available technique (12,13). The use of the techniques recommended by Maruschak et al. (14) and Nadeau and Noble (15) for performing thermodilution cardiac outputs should give reproducible and accurate data. Thermodilution cardiac output measurements in the presence of surgically created pulmonary and tricuspid insufficiency have been evaluated in animal models and in spite of these lesions are reliable enough to determine trends in cardiac performance (16). No catheter-induced distortion of valve anatomy resulting in significant valvular insufficiency has been identified (17). Cardiac output determined by thermodilution should reflect the true hemodynamic state, provided that the intracardiac and extracardiac shunts are closed, that cardiac output is not extremely low or regurgitant, and that all venous return is passing through the catheterized artery or conduit (15,18).

In addition to thermodilution cardiac output data, continuous observation of PA pressures provided by the PA catheter can provide an early warning of developing problems. We have observed in a number of cases an acute rise in PA pressure that was not immediately reflected in CVP. Because small children

have much more responsive pulmonary vascular systems than adults (19), pathophysiologic events are often rapidly followed by increases in PA pressures. The measurement of these pressures before cardio-pulmonary bypass allows comparisons with the acute hemodynamic responses after cardiac repair. The need for transthoracic right atrium and left atrium catheters is reduced by having a PA catheter in place. The risks of hemorrhage after transthoracic line removal is also eliminated by the use of percutaneous placed lines (5). Postoperative catheter removal also provides the opportunity to measure any residual right-ventricle—PA pressure gradient.

In summary, we have demonstrated that the placement of PA catheters in our young cardiac patients (a) can provide access to valuable cardiovascular data, (b) can be accomplished within a reasonable period of time, and (c) is not associated with excessive complications. Although new noninvasive techniques for monitoring cardiac performance such as echocardiographic and impedance methods are currently being evaluated for use in children (20), we believe that the risk-to-benefit ratio demonstrated in our patients supports the continued use of PA catheters in selected children undergoing cardiac surgery.

The authors thank Victor Moore, MD, for his continued wisdom and support.

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Letters to the Editor

Epidural Blood Patch: A Rapid Coagulation Response

Key Words: BLOOD, COAGULATION. COMPLICATIONS, HEADACHE—epidural patch.

To the Editor:

Postspinal headache can be treated with autologous blood patch placed into the epidural space. The ability of this epidural blood patch to relieve postlumbar puncture headache accounts for the mechanism of action but not the speed of the clinical response (1). In a controlled model simulating the mixing of blood and cerebrospinal fluid (CSF) at a dural leakage site, we have found that a clot forms in an average of only 22 s. This is some four times faster than even an activated clotting time.

Method. A Litton Datamedix Thromboelastograph D (TEG)2 was set up according to manufacturer's instructions and used to record the coagulation of unmixed blood and of a CSF-blood mixture. Cerebrospinal fluid and blood samples were obtained from six animals, with 360 μ L of blood being placed in a TEG coagulation pot and 180 μ L of blood followed by 180 μ L of CSF mixed in a similar pot. These were placed in the TEG and recording was simultaneously begun at a paper speed of 2 mm/min.

Results. The results are summarized in Table 1. Variables measured using a TEG include R, which represents onset and formation of the clot via proliferation of coagulation factors, the K-value, which represents the strengthening of the clot by intrinsic plasma and platelet factors, and the R+K value, which is equivalent to the clotting time. MA and

 α -angle were measured, the former representing maximal elasticity of the clot and the latter clot formation rate.

The R, K, and R + K values all showed significant decreases, indicating an effect on coagulation and platelet factors (2). Acceleration of the onset of coagulation and a stronger clot were observed.

Discussion. It appears that when CSF and blood mix, an acceleration of the coagulation cascade occurs. A previously demonstrated procoagulant activity of CSF has generally involved CSF altered by disease processes, pooled samples, and coagulation activity of hemorrhage into CSF (3). We used individual CSF samples and blood from healthy animals without coagulation abnormalities. We used a TEG that allowed us to show that it is mostly the R-time that is affected in the formation of clot. In a previous study, epidural blood patches were tested for leaks at a wide range of CSF pressures, and, on examination of the puncture site in the dural samples, some plugs were described (4). We have observed a rapidity of clotting more in keeping with the nearly immediate relief of spinal headache treated with epidural blood patches, and suggest that there may be coagulation at this interface of blood and CSF that causes almost instantaneous formation of a plug. We believe the reproducibility of our results, not seen in some previous studies, can be attributed to careful control of the experimental model. Human in vitro studies are planned.

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Table 1. Effect of Autologous Cerebrospinal Fluid on Coagulation of Canine Blood

	R	K	R + K	α-Angle	MA
n	6	6	6	6	6
Blood alone	12.83 (2.79)	8.17 (1.34)	21.00 (2.77)	61.50 (5.80)	59.33 (7.54)
CSF/blood mean	0.75 (0.80)	2.75 (1.15)	3.50 (1.50)	66.00 (5.72)	68.83 (6.09)
% of blood value	5.84	33.67	16.67	107.32	116.01
Data paired					
t ·	10.78	7.83	18.71	-1.70	-4.57
P	< 0.001	< 0.001	< 0.001	<0.5	< 0.01

Standard deviations in parentheses.

R, represents onset and formation of the clot via proliferation of coagulation factors; K, represents strengthening of the clot by intrinsic plasma and platelet factors; R + K, equivalent to the clotting time; α -Angle, clot formation rate; and MA, maximal elasticity of the clot.

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Intravenous Injection of Liquid Halothane

Key Words: ANESTHETICS, volatile—halothane. TOXICITY, halothane—pulmonary.

To the Editor:

Dwyer and Coppel's report describing the intravenous injection of liquid halothane (1) is of great interest, although I believe their emphasis on pulmonary vasculitis as the cause of their patient's fatal course may be misplaced. Rather, the clinical course and the microscopic findings at autopsy are typical of nonspecific acute pulmonary capillary leak syndromes and adult respiratory distress syndrome (ARDS) (2). The initial right heart strain is unlikely to have been due to fixed "damage to pulmonary vessels." Studies indicate (3,4) that 50%-66% of the cross-sectional area of the pulmonary vasculature must be obliterated (typically an acute saddle embolus or multiple pulmonary emboli) in order that right heart strain occur on the basis of mechanical obstruction to flow. The microscopic pathology in their patient ("some small areas of hemorrhagic infarction with small organizing thrombi. . . . Some small pulmonary vessels had areas of fibrinoid necrosis") (1) is not consistent with this. Moreover, the pulmonary vascular hemodynamics described show that changes in pulmonary vascular resistance were reactive and reversible, i.e., functional rather than fixed. This is more consistent with toxic vasoconstriction due to endothelial exposure to intravenous halothane, or a manifestation of hypoxic pulmonary vasoconstriction (5) resulting from capillary-leak pulmonary edema. Pulmonary vascular resistance (PVR) is frequently elevated in ARDS (6-9), correlates inversely with right ventricular ejection fraction (6,7), and has been shown to be the only parameter that separated nonsurvivors from survivors (9). Thus, elevated PVR and severe hypoxemia are common findings in severe pulmonary capillary leak syndromes of virtually any etiology.

In their management of the patient's hemodynamic deterioration, prostaglandin E₁, with the most favorable pulmonary to systemic ratio of all the currently available vasodilators used to treat pulmonary hypertension, would have been perhaps a more logical option than prostacyclin for treating the patient's increased PVR. Later in the course of management of this patient, dopamine administration

was increased to near pure alpha ranges, raising systemic vascular resistance without increasing blood pressure or cardiac output. Therapy might instead have been directed more toward improving cardiac output, e.g., with a β -agent such as epinephrine, combined with intraaortic balloon counterpulsation (10), with or without added prostaglandin E_1 to treat the increased PVR.

The mechanism of intravenous halothane toxicity remains unclear. From the data available, however, the result is a clinical syndrome of severe ARDS, no different from that common to many other critical illnesses. The role of pharmacologic manipulation of PVR in ARDS and septic shock is yet to be determined (9,11).

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Prophylactic Epidural Blood Patch in Obstetrics

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—blood patch.

To the Editor:

Colonna-Romano and Shapiro (1), in their study on the effectiveness of prophylactic epidural blood patching in obstetric patients, found a reduction in the incidence of moderate and severe postdural puncture headaches in the prophylactically treated patients. Three of the 19 patients in

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the treatment group that received a prophylactic blood patch through an existing epidural catheter eventually required a therapeutic epidural blood patch, in contrast to 7 of 20 patients in the routine management group. They conclude on the basis of this study that "because of its simplicity, efficacy, and freedom from complication, this technique is recommended in the prevention of postdural puncture headache of this type."

The data presented do not support such a far-reaching conclusion. Assume that the two groups are equal in all other respects. Approximately 7 of the 19 patients in the treatment group, if not treated with a prophylactic epidural blood patch, would be predicted to eventually require a therapeutic blood patch. Presumably, the remaining 12 patients would not have required such a procedure and therefore received an unnecessary prophylactic patch through the epidural catheter. In addition, three of the predicted seven patients eventually required a therapeutic blood patch despite receiving the prophylactic patch. Thus, by looking only at patients with a postdural puncture headache severe enough to require invasive treatment, the data reveal that 15 patients underwent an unnecessary prophylactic patch in order to save four patients from a therapeutic blood patch. The four "saved" patients actually traded a therapeutic epidural blood patch for a prophylactic patch through an existing epidural catheter.

The authors have outlined the benefits—including a reduction in the number of therapeutic epidural blood patches with their attendant risks, and possibly a reduction in the severity of headache. But what are the risks of a prophylactic blood patch? Clearly, the procedure is not without risk. Patients have been reported to suffer from backache, radiculopathy, and neck stiffness (2,3). Other as yet undefined risks include infection and arachnoiditis. Until the risks are better defined, the aggressive recommendations of the authors must be regarded with some concern.

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In Response:

Dr. Woodworth has brought up two different issues in his letter. One is the advisability of a prophylactic epidural blood patch in obstetrics, and the other is the safety of the same.

In our study (1) we tested the effectiveness of the prophylactic blood patch and concluded that the patch is indeed successful in preventing postdural puncture headache. Only 21% in the prophylactically treated group de-

veloped headache from a predicted 80% (control group). Therefore, of 10 patients two (20%) received an unsuccessful prophylactic patch, two (20%) a useless one (they did not need it), and six (60%) benefited from the patch.

Whether or not this 60% success rate is convincing evidence (we think it is) for the prophylactic patching of our patients is a matter of opinion. On the one hand, we know that their headaches will eventually fade away (regardless of our therapy); on the other, we are aware of their physical and psychological discomfort (not to mention how much a new mother dislikes to be confined in bed!).

The safety issue has already been addressed in the literature. No long-lasting morbidity has ever been reported (2), and the few cases of transient morbidity have never been demonstrated to be a consequence of the prophylactic patches (3,4).

After unintentional dural puncture with a large-gauge needle, the final decision to patch prophylactically the parturient should rest with the mother once she has been informed of the risks and benefits. As physicians, we should point out the safety and effectiveness of this procedure

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Ordinal Data Are Not Interval Data

Key Words: STATISTICS, ORDINAL AND INTERVAL DATA.

To the Editor:

I enjoyed reading the work of Atchison et al. (1), which added to my understanding of hypobaric spinal anesthesia. I wish to disagree, however, with their use of the mean and standard deviation to summarize the maximum level of anesthesia.

Dermatomal levels are *ordinal* data, not to be confused with interval data (also known as continuous data) (2,3). In addition, however, the greater the cephalad extent of the sensory level of spinal or epidural anesthesia, the *lower* the thoracic dermatome number. It is, therefore, best not to describe a maximum level of anesthesia as "T4.5 \pm 2.3 dermatomes." For example, a level of T10 is not twice as

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high as T5, nor is a level of T3 one-third as high as T9. The increase in the extent of spinal or epidural anesthesia when it goes from T11 to T10 is not necessarily the same as when a similar increase, from, say, T3 to T2, is seen. Furthermore, there is no such sensory level as T0 (zero); in fact, after the last thoracic dermatome, lumbar and then sacral dermatomes take over. Had one of their patients had a lumbar level, how would the authors have averaged in an L2 with their thoracic dermatomal levels?

Confusing ordinal with interval data is not rare. It is most commonly made in anesthesia literature when an author attempts to summarize data on Apgar scores or visual analogue scales. A similar example involves summarizing the ASA physical status of a group of patients with a mean and standard deviation (4): for example, "PS 2.79 \pm 0.55." One should remember that there is no such thing as a PS 0, that a PS 3 is not three times sicker than a PS 1, and that no one describes a single patient as being PS 2.79. My personal preference is to use Roman numerals when working with ordinal data, (e.g., PS II, dermatomal level T IX) to remind myself that the data do not have the same content as interval or continuous data.

Ordinal data can be summarized using a median to describe central tendency and percentiles to describe variability, instead of the more familiar mean and standard deviation. Alternatively, a frequency histogram nicely describes the data.

It is also not optimal to compare, as did Atchison et al., the means of two groups of ordinal data using the *t*-test, which was designed for interval data. The maximum level of spread would better have been compared between the two groups using a test such as the Mann–Whitney rank sum test.

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Prior Gastric Surgery and the Risk of Regurgitation

Key Words: COMPLICATIONS, ASPIRATION. LUNG, ASPIRATION.

To the Editor:

Regurgitation of stomach contents after induction of anesthesia is an event feared by anesthesiologists. To minimize the likelihood of its occurrence, and the sequel of pulmonary aspiration, there is great emphasis in preoperatively identifying patients who are at risk. Traditionally, it has been held that risk factors include obesity, pregnancy, hiatus hernia, use of certain drugs, nonfasting, or obtunded conscious states (1). Furthermore, adequate fasting time is no guarantee of an empty stomach as gastric emptying may be impaired in certain states (pregnancy) and diseases (recent trauma, insulin-requiring diabetes mellitus [2]). Finally, gastric insufflation of gases accompanying bag-mask ventilation due to poor technique or a "difficult airway" also increases risk of regurgitation (3). We report a case of regurgitation occurring upon induction of anesthesia in a patient who had undergone gastric surgery many years previously.

An &1-yr-old man, ASA physical status III, was scheduled for left-sided extracapsular cataract extraction and implantation of an intraocular lens under general anesthesia. His medical history was significant for a partial gastrectomy (Polya type) 22 yr earlier for a duodenal ulcer. There were no gastrointestinal symptoms. The patient reported annual episodes of bronchitis and there was a 60-pack-year history of smoking. Medications included an albuterol inhaler and choline theophyllinate syrup. Physical examination was unremarkable except for a hyperinflated chest with some mild wheezing detected on auscultation. Premedication was with 20 mg oral temazepam and 10 mg metoclopramide, 1 h before anesthesia.

In the operating room, electrocardiographic and pulse oximetry monitoring was started while a peripheral vein was cannulated. Preoxygenation was commenced, and a "priming" dose of vecuronium, 1 mg, was given intravenously. After several minutes, 120 mg propofol was given intravenously. After loss of consciousness, 7 mg vecuronium was given. At the onset of apnea, gentle bag-mask ventilation was begun. There was no difficulty with ventilation and chest-wall excursion appeared normal. Within 1 min of manual ventilation the patient began to cough weakly. Ventilation continued, and the coughing subsided after approximately 30 s as paralysis ensued. When no twitches could be detected with a peripheral nerve stimulator, laryngoscopy was performed. It was then discovered that the pharynx contained a small quantity of bile. Visualization of the larynx was easy and droplets of bile could be seen within the tracheal lumen. The pharynx was quickly suctioned and the trachea intubated. Bilateral breath sounds could be auscultated and wheezing was absent. Pulmonary compliance was estimated to be normal and the arterial oxygen saturation remained 99% throughout the entire procedure. A nasogastric tube was passed and the stomach evacuated of biliary fluid. Because there had been no signs of significant pulmonary aspiration, after discussion with the ophthalmologist it was decided to proceed with surgery.

The remainder of the anesthetic was uneventful. After full return of neuromuscular function, the patient was awakened in the lateral position and the trachea was extubated. The patient was transferred to the recovery room while breathing oxygen via a face mask. A chest radiograph was unchanged from the preoperative film. Pulse oximetry was continued in the recovery room, and the arterial oxygen saturation remained unchanged. Recovery was uneventful.

Reflux of bile into the gastric remnant is common after a Polya gastrectomy. In conscious patients, occasionally an associated reflux of bile into the esophagus occurs, with a subsequent "alkaline esophagitis" (4). Unfortunately, biliary reflux may be asymptomatic in some patients. Unconscious patients who have previously undergone Polya gastrectomy have increased risk of regurgitating bile into the pharynx. This is especially so if there is any delay in gastric emptying of liquids. Unfortunately, there is little information about the consequences of aspiration of bile, unaccompanied by acid or solids, into the lung. Nonetheless, the anesthesiologist is obliged to use an anesthetic technique designed to minimize the likelihood of regurgitation of bile in patients who have had a previous gastrectomy.

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Desipramine Potentiates Anesthetic and Lethal Effects of Ketamine

Key Words: ATARACTICS, ANTIDEPRESSANTS, TRICYCLIC—desipramine. ANESTHETICS, INTRAVENOUS—ketamine.

To the Editor:

Bruce and Capan (1) have reported no increased lethality of ketamine in mice treated with amitriptyline and tranylcypromine. To our knowledge, there have been no studies of the interaction of desipramine (DMI), a selective inhibitor of norepinephrine reuptake, and ketamine, which is also thought to inhibit norepinephrine reuptake and to be a weak releaser of norepinephrine (2,3).

In our protocol, approved by our Animal Use Committee, rats treated intraperitoneally with 10-20 $mg \cdot kg^{-1} \cdot day^{-1}$ of DMI in normal saline (2 mL/kg) or an equivalent amount of vehicle for either 2 or 28 days were anesthetized with ketamine to perform cisternal puncture for collection of cerebrospinal fluid for other purposes. Anesthesia was defined as lack of response to tail pinch. The high dose of DMI used was given because rodents are known to metabolize drugs at a higher rate than humans. Barkai et al. (4) found a mean plasma DMI level of 143 ng/mL in rats, which is a typical therapeutic level in humans, 24 h after the last intraperitoneal dose of 20 mg·kg⁻¹·day⁻¹ for 7 days. As shown in Table 1, animals treated with DMI required significantly less ketamine to achieve anesthesia. Before the interaction was recognized, two DMI-treated animals died of ketamine doses (150 mg/kg) insufficient to anesthetize the placebo-treated animals. In the study by Bruce and Capan (1), no animals died at a dose less than 400 mg/kg.

The present observations suggest a potentiation of ketamine by DMI. The negative results in the study by Bruce and Capan may be due to insufficient serum levels of the drugs given, as their animals were given human doses of

Table 1. Mean Ketamine Dose Required for Anesthesia

	No. of	Ketamine dose (mg/kg) ^a		
Treatment group	animals	Mean ± sem	Range	
Placebo—2 days	13	201 ± 8	167–254	
DMI—10 mg·kg ⁻¹ ·day ⁻¹ for 2 days	10	120 ± 2^b	111-133	
DMI—20 mg·kg ⁻¹ ·day ⁻¹ for 2 days	5	107 ± 24^{c}	70-203 ^d	
Placebo—28 days	11	180 ± 7*	166248	
DMI-10 mg·kg ⁻¹ ·day ⁻¹ for 28 days	13	$90 \pm 2^{b,e}$	83115	

Ketamine was give intraperitoneally, initial dose of 125 mg/kg in placebo rats, 75 mg/kg in desipramine-treated rats with additional doses of 5–10 mg given every 10 min if anesthesia not achieved. ⁵P > 0.001 compared with placebo.

 $^{^{\}circ}P = 0.014$ compared with placebo.

⁴Actual values: 70, 84, 88, 90, 203.

Lower requirement for anesthesia in chronically treated animals is probably related to lower stress levels resulting from previous exposure to the stressful stimulus (5).

drug (1–4 mg·kg⁻¹·day⁻¹ of amitriptyline orally or 0.125–0.5 mg·kg⁻¹·day⁻¹ orally of tranylcypramine), which the literature suggests would lead to serum levels in rats approximately 10% of the levels achieved in humans given the same doses. Our findings suggest that there may be an important potentiation of the anesthetic effect of ketamine by DMI, one that needs further study.

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Book Reviews

Medicine for Anaesthetists

M. D. Vickers and R. M. Jones, eds. 3rd ed. Boston: Blackwell Scientific Publications, 1989, 600 pp, \$119.95.

Many physicians can practice clinically competent medicine on a daily basis with only superficial understanding of the most basic principles of anesthesia. However, anesthesiologists, whose training is rooted in pharmacology and physiology, must be skilled physicians with expertise in almost every branch of medicine if they are to be deemed competent to anesthetize safely all patients. With the expanding volume of medical subspecialty knowledge, there arises a need for a text that offers the anesthesiologist a concise review of medical diseases with a focus on what a problem is and what it means in terms of function. To meet this need, the editors of Medicine for Anaesthetists have assembled a collection of 18 chapters that mirror those found in more voluminous textbooks of internal medicine. A generous portion of the book is appropriately devoted to cardiovascular, pulmonary, and renal concerns, and with the addition of a "Gastrointestinal Disorders" chapter in the third edition, all major organ systems are thoughtfully represented without any gross imbalances of emphasis. There is a section dealing with the pregnant patient with concomitant disease; however, chapters covering the more common geriatric and pediatric problems of importance to the anesthesiologist might also have been appreciated in this revision. In addition, the newly added chapter on tropical diseases, although certainly interesting reading, seems a bit out of place in a text that eliminates its bulkiness by concentrating on the more common illnesses of everyday practice.

The usefulness of this endeavor lies in its concise, logical presentation of the material at hand. Each chapter is preceded by an in-depth outline of its contents, which makes for rapid identification of a specific issue. The style of writing is uniform and direct and will be gratefully acknowledged by a hurried reader who must prepare for an upcoming case. Tables are plentiful and generally contain classification schemes that can be scanned at a glance. References, although not exhaustive (and they are, inexplicably, absent from a chapter or two), for the most part go above and beyond that which is contained in the anesthesia literature and afford the chance for a more profound scrutiny than the text can supply.

If there tends to be a bias on the part of this reviewer, it

would have been in favor of more space allocated to discussions of the anesthetic considerations. There is a suitable amount of information offered concerning the clinical presentations, pathophysiology, and medical treatments of the coexisting diseases. However, a more systematic approach to preoperative risk assessment and preparation, intraoperative management issues, and potential postoperative pitfalls would have greatly strengthened this text. The preface states that this text was not intended to be just another short textbook of medicine, but in many ways the book is an economical alternative to some of the more lengthy volumes that one keeps on the shelf as medical reference texts. As such, it is recommended to all anesthesiologists who find themselves in need of a review of medical subspecialty knowledge.

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Anesthesiology Clinics of North America: Infection in Anesthesia

Arnold J. Berry, ed. Philadelphia: W. B. Saunders, 1989, 234 pp, \$27.00 for a single issue or \$65.00 for an annual subscription of four issues.

The explosive impact of the acquired immunodeficiency syndrome (AIDS), its exponential growth and spread, and the devastating morbidity and mortality engendered have brought about a new awareness of infectious diseases and of their importance in modern health care. The anesthesiologist does not exist or practice in a vacuum, and the viral, bacterial, and protozoan diseases about him affect his patient care, methods of practice, and the worries that plague him concerning contamination and infection of himself and his family. This is foreign territory to most anesthesiologists, cavernous, dimly lit, poorly charted, and full of traps and snarls, ever ready to surprise the unwary.

Dr. Arnold Berry has recruited an excellent group of knowledgeable scientists and physicians to create a primer on infectious diseases for the anesthesiologist. However, the result is uneven, with some contributions providing a cornucopia of information that spills out in verbose abundance—much of it relevant, and yet often an excess to the practicing clinical anesthesiologist. This work seeks to be both a primer and a reference book—and it gets lost somewhere in between the two.

Articles on community-acquired respiratory-tract infection, septic shock, and immunologic changes associated with anesthesia and surgery are overflowing with data, which the practitioner may find burdensome and impractical. The effect of these diseases on anesthetic management receives no consideration, and the value of the presentations to the clinician is thus markedly diluted.

The chapter on AIDS begins in a well-written way and seems replete with interesting background and useful clinical information. But after managing to whet the reader's appetite, the authors suddenly come to a halt, as if they had run out of words, with much left unsaid. This wondrous meal still leaves us hungry. The anesthetic implications and management considerations of opportunistic infections such as pneumocystis, tuberculosis, cytomegalovirus, and others receive no consideration, and there is no section on preoperative evaluation and preparation. Clinicians may well wonder why there is such a detailed description of the human immunodeficiency virus infrastructure and yet such a sparsity of practical clinical information regarding anticipated problems and anesthetic management of the patient with AIDS.

Chapters on sterilization, disinfection, and decontamination of anesthesia equipment are informative and useful, and provide important information not otherwise readily available.

Dr. Berry's article on infection control in anesthesia is of practical import and provides an interesting analysis of its problems, together with important guidelines that should be incorporated into a "policies and procedures" manual of every anesthesia department.

The book seems oriented to critical care physicians, rather than to operating room practitioners of anesthesiology and, as such, will probably find a more receptive audience in the intensive care unit than in the operating room.

This interesting effort is well-edited, if poorly focused, and reads easily. It is half primer, half reference, and fully neither one: it contains at times a surfeit of facts, at times a paucity of practicality. It is strictly for those with a major interest in the area and a lot of time to indulge themselves.

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Problems in Anesthesia: Neuromuscular Relaxants

Stephen M. Rupp, ed. Philadelphia: J. B. Lippincott, 1989, 147 pp, \$16.00 for a single issue or \$55.00 for an annual subscription of four issues.

This book is devoted entirely to the problems encountered during the clinical use of muscle relaxants and their antagonists. It is known that the neuromuscular blocking drugs and the reversal agents do exert actions on sites other than the neuromuscular junction (other nicotinic, muscarinic receptors and nonspecific targets, e.g., mast cells). These actions are generally undesirable stimulating or inhibitory side effects. In addition, because the response to relaxants is variable or unpredictable in the population at large or may be adversely modified by perioperative medication and/or disease states, monitoring neuromuscular function is important to avoid problems of improper dosing.

Seventeen authors have contributed 12 chapters that cover most of the above-mentioned considerations. The first chapter outlines in a simple and lucid presentation the practical aspects of monitoring neuromuscular function as the cornerstone for using these muscle relaxants. The authors emphasize the importance of providing optimal surgical conditions and of ensuring timely restoration of neuromuscular function. This would improve patient safety, increase the efficient utilization of operating rooms, and prevent backlog in recovery rooms.

The second chapter deals with problems associated with the routine use of succinylcholine in pediatric patients; these range from masseter spasm and malignant hyperthermia to cardiac dysrhythmias, myoglobinuria, and hyperkalemia, especially in patients with undiagnosed muscular dystrophy. The author believes that the usefulness of succinylcholine is limited by its side effects and recommends that the anesthesiologist always have it available but avoid using it in the presence of the new intermediate-acting relaxants.

Antagonism of profound neuromuscular blockade is the theme of the third chapter. The author analyzes the incidence of unsuspected residual curarization as it relates to the degree of neuromuscular blockade before antagonism. He answers several questions of great interest to anesthesiologists: for example, what level of spontaneous recovery will predict adequate reversal of neuromuscular blockade? and can edrophonium, neostigmine, and pyridostigmine be used interchangeably with regard to the level of neuromuscular block or the type of muscle relaxant used (intermediate vs long-acting relaxants)? Although the chapter on infusion of relaxants may appear out of place, titration of neuromuscular relaxants to effect by infusion, as recommended here, will avoid the peaks and valleys of drug concentration associated with bolus dosing. The latter will tend toward periods of overdose with prolonged recovery or periods of less optimal surgical conditions. In addition, titrating the relaxant by infusion will make it possible to identify and compensate for increased sensitivity to the relaxant or decreased clearance early in the course of the anesthetic.

The chapters that follow deal with controversial issues such as priming, relaxants in patients with increased intracranial pressure, and malignant hyperthermia susceptibility, with emphasis on the incidence of masseter spasm and its clinical significance. Another chapter addresses the problem of prolonged response to succinylcholine. The last four chapters are devoted to problems related to certain

pathological and surgical conditions, i.e., thermal injury, hepatic and renal failure, and, finally, open-eye surgery.

The 12 chapters vary in style and content, and, apart from some typographical errors and some incorrect citations of references, on the whole they are reasonably integrated and informative. The book is particularly useful to practitioners seeking answers to controversial issues cited throughout the various chapters.

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Principles of Applied Biomedical Instrumentation, 3rd Edition

L. A. Geddes and L. E. Baker, eds., New York: John Wiley & Sons, 1989, 961 pp, \$64.95.

Over the past decade there has been a rapid expansion of the application of biomedical instruments to the practice of clinical anesthesia. Many of these developments have come in the way of invasive and noninvasive monitoring devices. For an anesthesiologist to use this information properly it is important that he or she understand the underlying principles on which the devices are based. Principles of Applied Biomedical Instrumentation is in its third edition because it has been a useful resource to biomedical engineers and medical personnel involved in the technical aspects of clinical or research medicine. Biomedical instrumentation falls into three categories: diagnostic, therapeutic, and assistive devices. The majority of devices fall into the category of diagnostic; these devices differ primarily in the physical principle employed by their transducer. A transducer is a device that receives a physiologic signal by some transducible physical phenomena and converts it into an electrical signal. For this reason Principles is divided into sections according to the physics involved in each type of transducer, i.e., resistive transducers, photoelectric transducers, chemical transducers. Each of these chapters first presents the basic physics involved followed by significant detail regarding the materials and methods of construction and limits of accuracy of the specific transducers. Although the authors stress that a strong background in mathematics is not required and that the book presents few complex equations there is an assumption that the reader has a basic understanding of simple electrical circuits in many of the discussions. In short, if you are familiar with a Wheatstone bridge, the electronics presented in the Principles will not be a problem for you. This edition has added chapters discussing ventilators and anesthesia. These chapters are extremely basic from an anesthesiologist's point of view relative to the extensive and detailed description presented in other chapters. For example, the chapter on anesthesia and anesthesia equipment is only 15 pages, whereas the

chapter on detecting physiologic events by impedance is 115 pages. Although the authors illustrate many of the principles by giving clinical examples of the applications of these principles in biomedical instrumentation, many of these applications are more related to specific uses for individual research studies as opposed to accepted routine clinical instruments. Nevertheless, many of the discussions of the principles and applications of devices are excellent and will give the reader a firm understanding of not only how devices work but, more important, the limitations of each type of transducer in detecting a physiologic event. The book concludes with a chapter entitled "Criteria for Faithful Reproduction of an Event." This chapter gives an interesting overview of how analog systems display physiologic signals, one that starts with a discussion of Fourier analysis and concludes with a discussion of dynamic frequency response.

For most clinical anesthesiologists, parts of this book may contain an excessive amount of detail, but this makes for completeness. This book is not a replacement for any of the currently available texts on anesthetic equipment or physics for the anesthetist. The *Principles* is an excellent reference text for anesthesiologists with a moderate technical background and for those involved in research where an understanding of biomedical instrumentation is essential. This text will give the reader an appreciation for the ingenuity and complexity involved in developing biomedical instrumentation from the basic physical principles to the specifics of technical design.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Bendetti C, Chapman CR, Giron G, eds. *Opioid Analgesia*. Volume 14 in Advances in Pain Research and Therapy. New York: Raven Press, 1990, 466 pp, \$98.00.

Kalenda Z. Mastering Infrared Capnography. Ziest, The Netherlands: Kerckebasch, BV, 1990.

Lake CL, ed. Clinical Monitoring. Philadelphia: W.B. Saunders, 1990, 850 pp, \$95.00.

Rawal N, Coombs DW, eds. Spinal Narcotics. A volume in the Current Management of Pain Series. Boston: Kluwer Academic Publishers Group, 1990, 147 pp, \$71.95.

Roizen MF, ed. Anesthesia for Vascular Surgery. New York: Churchill Livingstone, 1990, 505 pp, \$75.00.

Steward DJ. Manual of Pediatric Anesthesia, 3rd ed. New York: Churchill Livingstone, 1990, 445 pp, \$29.95.

Tyler DC, Krane EJ, eds. *Pediatric Pain*. Volume 15 in Advances in Pain Research and Therapy. New York: Raven Press, 1990, 404 pp, \$95.00.

Wood M, Wood AJJ, eds. *Drugs and Anesthesia, Pharmacology for Anesthesiologists*. 2nd ed. Baltimore: Williams and Wilkens, 1990, 67 pp, \$75.00.

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1990 AWARDS

At the IARS 64th Congress in March 1990, the Board of Trustees announced recipients of the 1990 Award as follows:

Brian G. Bertha, MD, Mayo Clinic, Rochester, MN:

"Do Inotropic and Vasopressor Drugs Stimulate or Attenuate Platelet Aggregation and Thrombosis in Pig Coronary Arteries?"

Karen B. Domino, MD, University of Washington Harborview Medical Center, Seattle, WA:

"Effect of Changes in PCO₂ on the Matching of Ventilation and Perfusion in Normal and Edematous Lungs"

Roderic G. Eckenhoff, MD, University of Pennsylvania Medical Center, Philadelphia, PA:

"Subcellular Distribution of Inhalational Anesthetics"

Robert Allen Pearce, MD, PhD, University of Wisconsin, Madison, WI: "Effect of Volatile Anesthetics on Neuronal Inhibition in the Rat Hippocampus In Vitro"

Christoph Stein, MD, Ludwig-Maximilians-Universitat, Munich, West Germany: "Peripheral Opioid Receptors Mediating Antinociception in Inflammation: Endogenous Ligands"

David O. Warner, MD, Mayo Clinic and Mayo Foundation, Rochester, MN: "Volatile Anesthetics and Epithelium-Mediated Relaxation in Airway Smooth Muscle"

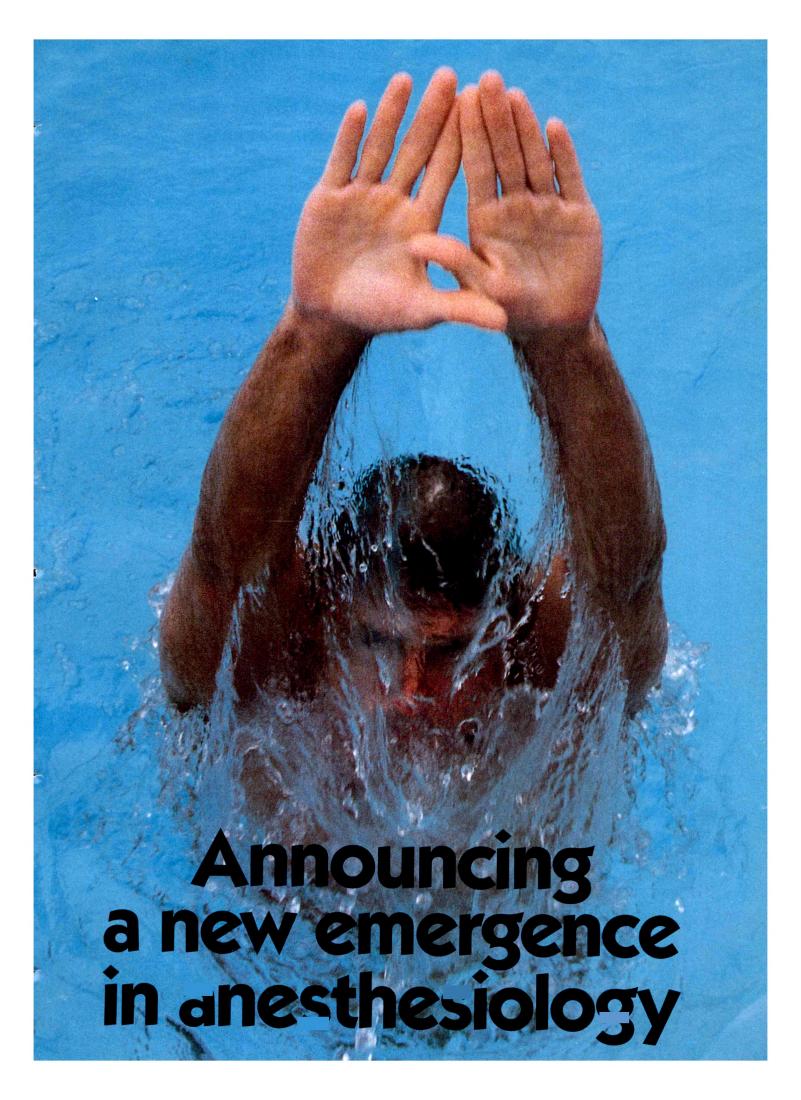
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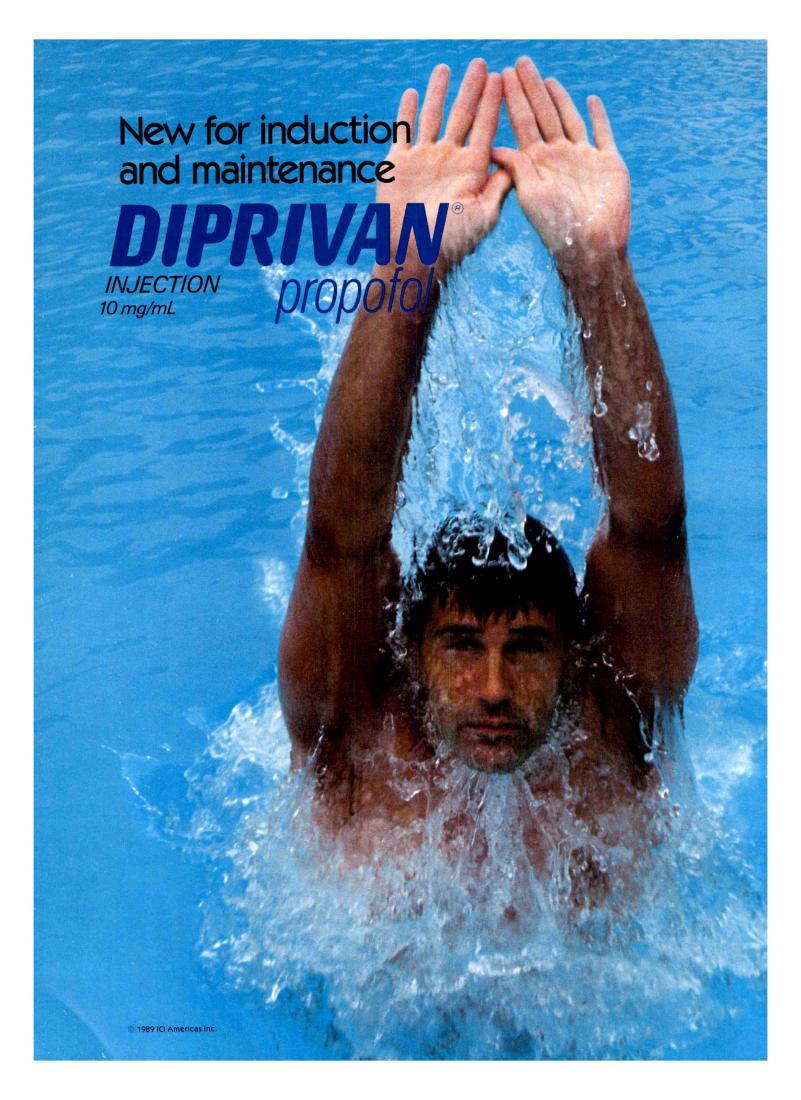
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- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

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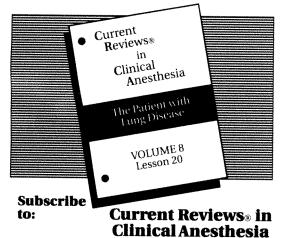
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